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(71) Applicant *(for all designated States except US)*: GENENTECH, INC. [US/US]; 1 DNA Way, South San Francisco, CA 94080-4990 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BAKER, Kevin, P. [GB/US]; 14006 Indian Run Drive, Darnestown, MD 20878 (US). GODDARD, Audrey [CA/US]; 110 Congo Street, San Francisco, CA 94131 (US). WOOD, William, I. [US/US]; 35 Southdown Court, Hillsborough, CA 94010 (US).

(74) Agents: KRESNAK, Mark, T. et al.; c/o Genentech, Inc., MS49, 1 DNA Way, South San Francisco, CA 94080-4990 (US).

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(54) Title: NOVEL POLYNUCLEOTIDES AND METHOD OF USE THEREOF

(57) Abstract: The present invention is directed to novel polynucleotides and to polypeptides encoded thereby. Also provided herein are vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide molecules comprising the polypeptides of the present invention fused to heterologous polypeptide sequences, antibodies which bind to the polypeptides of the present invention and to methods for producing the polypeptides of the present invention.

NOVEL POLYNUCLEOTIDES AND METHOD OF USE THEREOF

FIELD OF THE INVENTION

The present invention relates generally to the identification and isolation of novel nucleic acid molecules which constitute at least a portion of full-length cDNA molecules that encode human polypeptides.

BACKGROUND OF THE INVENTION

Extracellular proteins play important roles in, among other things, the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

Secreted proteins have various industrial applications, including as pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)].

Membrane-bound proteins and receptors can play important roles in, among other things, the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and

nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interactions. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. Efforts are being undertaken by both industry and academia to identify new, native receptor or membrane-bound proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor or membrane-bound proteins.

Recently, significant progress has been made in identifying and isolating unique nucleic acid moelcules which encode all or a portion of many mammalian proteins. We herein describe the identification and characterization of novel polynucleotides which constitute at least partial cDNA molecules that encode various human polypeptides.

SUMMARY OF THE INVENTION

Novel polynucleotides have been identified and isolated which constitute at least partial cDNA molecules that encode human polypeptides.

In one embodiment, the invention provides an isolated nucleic acid molecule comprising any one of the nucleic acid sequences shown in the accompanying figures, or the complement thereof, or polynucleotide variants of those nucleic acid sequences as defined below.

In another embodiment, the invention provides an isolated nucleic acid molecule consisting essentially of any one of the nucleic acid sequences shown in the accompanying figures, or the complement thereof, or polynucleotide variants of those nucleic acid sequences as defined below.

In another embodiment, the invention provides an isolated nucleic acid molecule consisting of any one of the nucleic acid sequences shown in the accompanying figures, or the complement thereof, or polynucleotide variants of those nucleic acid sequences as defined below.

In yet another embodiment, the invention provides an isolated nucleic acid molecule that comprises a nucleotide sequence having at least about 80% sequence identity, preferably at least about 81% sequence identity, more preferably at least about 82% sequence identity, yet more preferably at least about 83% sequence identity, yet more preferably at least about 84% sequence identity, yet more preferably at least about 85% sequence identity, yet more preferably at least about 86% sequence identity, yet more preferably at least about 87% sequence identity, yet more preferably at least about 88% sequence identity, yet more preferably at least about 89% sequence identity, yet more preferably at least about 90% sequence identity, yet more preferably at least about 91% sequence identity, yet more preferably at least about 92% sequence identity, yet more preferably at least about 93% sequence identity, yet more preferably at least about 94% sequence identity, yet more preferably at least about 95% sequence identity, yet more preferably at least about 96% sequence identity, yet more preferably at least about 97% sequence identity, yet more preferably at least about 98% sequence identity and yet more preferably at least about 99% sequence identity to (a) the DNA molecule of any one of Figure 1 to 562, or (b) the complement of the DNA molecule of (a).

In another aspect, the isolated nucleic acid molecule consists essentially of a nucleotide sequence having at least about 80% sequence identity, preferably at least about 81% sequence identity, more preferably at least about 82% sequence identity, yet more preferably at least about 83% sequence identity, yet more preferably at least about 84% sequence identity, yet more preferably at least about 85% sequence identity, yet more preferably at least about 86% sequence identity, yet more preferably at least about 87% sequence identity, yet more preferably at least about 88% sequence identity, yet more preferably at least about 89% sequence identity, yet more preferably at least about 90% sequence identity, yet more preferably at least about 91% sequence identity, yet more preferably at least about 92% sequence identity, yet more preferably at least about 93% sequence identity, yet more preferably at least about 94% sequence identity, yet more preferably at least about 95% sequence identity, yet more preferably at least about 96% sequence identity, yet more preferably at least about 97% sequence identity, yet more preferably at least about 98% sequence identity and yet more preferably at least about 99% sequence identity to (a) the DNA molecule of any one of Figure 1 to 562, or (b) the complement of the DNA molecule of (a).

In yet another aspect, the isolated nucleic acid molecule consists of a nucleotide sequence having at least about 80% sequence identity, preferably at least about 81% sequence identity, more preferably at least about 82% sequence identity, yet more preferably at least about 83% sequence identity, yet more preferably at least about 84% sequence identity, yet more preferably at least about 85% sequence identity, yet more preferably at least about 86% sequence identity, yet more preferably at least about 87% sequence identity, yet more preferably at least about 88% sequence identity, yet more preferably at least about 89% sequence identity, yet more preferably at least about 90% sequence identity, yet more preferably at least about 91% sequence identity, yet more preferably at least about 92% sequence identity, yet more preferably at least about 93% sequence identity, yet more preferably at least about 94% sequence identity, yet more preferably at least about 95% sequence identity, yet more preferably at least about 96% sequence identity, yet more preferably at least about 97% sequence identity, yet more preferably at least about 98% sequence identity and yet more preferably at least about 99% sequence identity to (a) the DNA molecule of any one of Figure 1 to 562, or (b) the complement of the DNA molecule of (a).

In another embodiment, the invention concerns an isolated nucleic acid molecule which comprises a nucleotide sequence that hybridizes to (a) the DNA molecule of any one of Figure 1 to 562, or (b) the complement of the DNA molecule of (a). Preferably, hybridization occurs under stringent hybridization and wash conditions. Also, it is preferred that the isolated nucleic acid molecule is fully complementary to (a) the DNA molecule of any one of Figure 1 to 562, or (b) the complement of the DNA molecule of (a).

In yet another embodiment, the present invention provides an isolated nucleic acid molecule which comprises at least about 10 consecutive nucleotides contained within (a) the DNA molecule of any one of Figure 1 to 562, or (b) the complement of the DNA molecule of (a) which may find use as, for example, hybridizing oligonucleotide probes or for encoding polypeptide fragments that may optionally comprise a binding site for an antibody. In particular aspects, the isolated nucleic acid molecule is from about 10 to about 1000, about 10 to about 900, about 10 to about 800, about 10 to about 700, about 10 to about 600, about 10 to about 500, about 10 to about 400, about 10 to about 300, about 10 to about 200, about 10 to about 100, about 10 to about 90,

about 10 to about 80, about 10 to about 70, about 10 to about 60, about 10 to about 50, about 10 to about 40, about 10 to about 30 or about 10 to about 20 nucleotides in length, where the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. In yet other aspects, the isolated nucleic acid molecule comprises at least about 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 consecutive nucleotides contained within (a) the DNA molecule of any one of Figure 1 to 562, or (b) the complement of the DNA molecule of (a).

The present invention is also directed to a method of using an oligonucleotide probe having a nucleotide sequence derived from a nucleic acid molecule described herein for detecting the presence of and/or obtaining a full-length mammalian cDNA molecule from a mammalian cDNA library which encodes a mammalian polypeptide. Preferably, the mammal is human. The methods comprise the step of screening a mammalian cDNA library with one or more of the herein described oligonucleotides to detect the presence of a full-length cDNA and, optionally, obtaining the full-length cDNA from that library.

In another embodiment, the invention provides a vector comprising any of the isolated nucleic acid molecules described herein or their variants.

A host cell comprising such a vector is also provided. By way of example, the host cells may be CHO cells, *E. coli*, or yeast. A process for producing polypeptides is further provided and comprises culturing the host cells under conditions suitable for expression of a polypeptide and recovering the polypeptide from the cell culture.

In another embodiment, the invention provides isolated polypeptides encoded by any of the isolated nucleic acids described herein, wherein thise polypeptides are herein designated as SRT polypeptides.

In yet another embodiment, the invention provides antibodies which specifically bind to a polypeptide encoded by a nucleic acid molecule described herein. Preferably, the antibodies are monoclonal antibodies.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a nucleotide sequence (SEQ ID NO:1) designated herein as DNA8284.

Figure 2 shows a nucleotide sequence (SEQ ID NO:2) designated herein as DNA8328.

Figure 3 shows a nucleotide sequence (SEQ ID NO:3) designated herein as DNA8350.

Figure 4 shows a nucleotide sequence (SEQ ID NO:4) designated herein as DNA8369.

Figure 5 shows a nucleotide sequence (SEQ ID NO:5) designated herein as DNA8377.

Figure 6 shows a nucleotide sequence (SEQ ID NO:6) designated herein as DNA8456.

Figure 7 shows a nucleotide sequence (SEQ ID NO:7) designated herein as DNA8555.

Figure 8 shows a nucleotide sequence (SEQ ID NO:8) designated herein as DNA8576.

Figure 9 shows a nucleotide sequence (SEQ ID NO:9) designated herein as DNA9383.

Figure 10 shows a nucleotide sequence (SEQ ID NO:10) designated herein as DNA9840.

Figure 11 shows a nucleotide sequence (SEQ ID NO:11) designated herein as DNA10028.

Figure 12 shows a nucleotide sequence (SEQ ID NO:12) designated herein as DNA10072.

Figure 13 shows a nucleotide sequence (SEQ ID NO:13) designated herein as DNA10242.

Figure 14 shows a nucleotide sequence (SEQ ID NO:14) designated herein as DNA10281.

Figure 15 shows a nucleotide sequence (SEQ ID NO:15) designated herein as DNA12628.

Figure 16 shows a nucleotide sequence (SEQ ID NO:16) designated herein as DNA12646.

Figure 17 shows a nucleotide sequence (SEQ ID NO:17) designated herein as DNA12655.

Figure 18 shows a nucleotide sequence (SEQ ID NO:18) designated herein as DNA12660.

Figure 19 shows a nucleotide sequence (SEQ ID NO:19) designated herein as DNA12668.

Figure 20 shows a nucleotide sequence (SEQ ID NO:20) designated herein as DNA12726.

Figure 21 shows a nucleotide sequence (SEQ ID NO:21) designated herein as DNA12728.

Figure 22 shows a nucleotide sequence (SEQ ID NO:22) designated herein as DNA12729.

Figure 23 shows a nucleotide sequence (SEQ ID NO:23) designated herein as DNA12732.

Figure 24 shows a nucleotide sequence (SEQ ID NO:24) designated herein as DNA12733.

Figure 25 shows a nucleotide sequence (SEQ ID NO:25) designated herein as DNA12741.

Figure 26 shows a nucleotide sequence (SEQ ID NO:26) designated herein as DNA12742.

Figure 27 shows a nucleotide sequence (SEQ ID NO:27) designated herein as DNA12747.

Figure 28 shows a nucleotide sequence (SEQ ID NO:28) designated herein as DNA12752.

Figure 29 shows a nucleotide sequence (SEQ ID NO:29) designated herein as DNA12797.

Figure 30 shows a nucleotide sequence (SEQ ID NO:30) designated herein as DNA12801.

Figure 31 shows a nucleotide sequence (SEQ ID NO:31) designated herein as DNA12802.

Figure 32 shows a nucleotide sequence (SEQ ID NO:32) designated herein as DNA12817.

Figure 33 shows a nucleotide sequence (SEQ ID NO:33) designated herein as DNA12819.

Figure 34 shows a nucleotide sequence (SEQ ID NO:34) designated herein as DNA12829.

Figure 35 shows a nucleotide sequence (SEQ ID NO:35) designated herein as DNA12830.

Figure 36 shows a nucleotide sequence (SEQ ID NO:36) designated herein as DNA12834.

Figure 37 shows a nucleotide sequence (SEQ ID NO:37) designated herein as DNA12837.

Figure 38 shows a nucleotide sequence (SEQ ID NO:38) designated herein as DNA12840.

Figure 39 shows a nucleotide sequence (SEQ ID NO:39) designated herein as DNA12841.

Figure 40 shows a nucleotide sequence (SEQ ID NO:40) designated herein as DNA12844.

Figure 41 shows a nucleotide sequence (SEQ ID NO:41) designated herein as DNA12846.

Figure 42 shows a nucleotide sequence (SEQ ID NO:42) designated herein as DNA12850.

Figure 43 shows a nucleotide sequence (SEQ ID NO:43) designated herein as DNA12865.

Figure 44 shows a nucleotide sequence (SEQ ID NO:44) designated herein as DNA12867.

Figure 45 shows a nucleotide sequence (SEQ ID NO:45) designated herein as DNA12884.

Figure 46 shows a nucleotide sequence (SEQ ID NO:46) designated herein as DNA12889.

Figure 47 shows a nucleotide sequence (SEQ ID NO:47) designated herein as DNA12891.

Figure 48 shows a nucleotide sequence (SEQ ID NO:48) designated herein as DNA12900.

Figure 49 shows a nucleotide sequence (SEQ ID NO:49) designated herein as DNA12922.

Figure 50 shows a nucleotide sequence (SEQ ID NO:50) designated herein as DNA12946.

Figure 51 shows a nucleotide sequence (SEQ ID NO:51) designated herein as DNA12967.

Figure 52 shows a nucleotide sequence (SEQ ID NO:52) designated herein as DNA12974.

Figure 53 shows a nucleotide sequence (SEQ ID NO:53) designated herein as DNA12982.

Figure 54 shows a nucleotide sequence (SEQ ID NO:54) designated herein as DNA12983.

Figure 55 shows a nucleotide sequence (SEQ ID NO:55) designated herein as DNA12991.

Figure 56 shows a nucleotide sequence (SEQ ID NO:56) designated herein as DNA12998.

Figure 57 shows a nucleotide sequence (SEQ ID NO:57) designated herein as DNA12999.

Figure 58 shows a nucleotide sequence (SEQ ID NO:58) designated herein as DNA13101.

Figure 59 shows a nucleotide sequence (SEQ ID NO:59) designated herein as DNA13104.

Figure 60 shows a nucleotide sequence (SEQ ID NO:60) designated herein as DNA13110.

Figure 61 shows a nucleotide sequence (SEQ ID NO:61) designated herein as DNA13114.

Figure 62 shows a nucleotide sequence (SEQ ID NO:62) designated herein as DNA13115.

Figure 63 shows a nucleotide sequence (SEQ ID NO:63) designated herein as DNA13116.

Figure 64 shows a nucleotide sequence (SEQ ID NO:64) designated herein as DNA13118.

Figure 65 shows a nucleotide sequence (SEQ ID NO:65) designated herein as DNA13124.

Figure 66 shows a nucleotide sequence (SEQ ID NO:66) designated herein as DNA13132.

Figure 67 shows a nucleotide sequence (SEQ ID NO:67) designated herein as DNA13133.

Figure 68 shows a nucleotide sequence (SEQ ID NO:68) designated herein as DNA13146.

Figure 69 shows a nucleotide sequence (SEQ ID NO:69) designated herein as DNA13152.

Figure 70 shows a nucleotide sequence (SEQ ID NO:70) designated herein as DNA13156.

Figure 71 shows a nucleotide sequence (SEQ ID NO:71) designated herein as DNA13163.

Figure 72 shows a nucleotide sequence (SEQ ID NO:72) designated herein as DNA13185.

Figure 73 shows a nucleotide sequence (SEQ ID NO:73) designated herein as DNA13992.

Figure 74 shows a nucleotide sequence (SEQ ID NO:74) designated herein as DNA14523.

Figure 75 shows a nucleotide sequence (SEQ ID NO:75) designated herein as DNA14656.

Figure 76 shows a nucleotide sequence (SEQ ID NO:76) designated herein as DNA14938.

Figure 77 shows a nucleotide sequence (SEQ ID NO:77) designated herein as DNA15172.

Figure 78 shows a nucleotide sequence (SEQ ID NO:78) designated herein as DNA15618.

Figure 79 shows a nucleotide sequence (SEQ ID NO:79) designated herein as DNA16546.

Figure 80 shows a nucleotide sequence (SEQ ID NO:80) designated herein as DNA16669.

Figure 81 shows a nucleotide sequence (SEQ ID NO:81) designated herein as DNA17244.

Figure 82 shows a nucleotide sequence (SEQ ID NO:82) designated herein as DNA18382.

Figure 83 shows a nucleotide sequence (SEQ ID NO:83) designated herein as DNA18444.

Figure 84 shows a nucleotide sequence (SEQ ID NO:84) designated herein as DNA18649.

Figure 85 shows a nucleotide sequence (SEQ ID NO:85) designated herein as DNA19597.

Figure 86 shows a nucleotide sequence (SEQ ID NO:86) designated herein as DNA19601.

Figure 87 shows a nucleotide sequence (SEQ ID NO:87) designated herein as DNA21386.

Figure 88 shows a nucleotide sequence (SEQ ID NO:88) designated herein as DNA22868.

Figure 89 shows a nucleotide sequence (SEQ ID NO:89) designated herein as DNA23694.

Figure 90 shows a nucleotide sequence (SEQ ID NO:90) designated herein as DNA24050.

Figure 91 shows a nucleotide sequence (SEQ ID NO:91) designated herein as DNA24074.

Figure 92 shows a nucleotide sequence (SEQ ID NO:92) designated herein as DNA24787.

Figure 93 shows a nucleotide sequence (SEQ ID NO:93) designated herein as DNA28242.

Figure 94 shows a nucleotide sequence (SEQ ID NO:94) designated herein as DNA28254.

Figure 95 shows a nucleotide sequence (SEQ ID NO:95) designated herein as DNA31751.

Figure 96 shows a nucleotide sequence (SEQ ID NO:96) designated herein as DNA32922.

Figure 97 shows a nucleotide sequence (SEQ ID NO:97) designated herein as DNA33439.

Figure 98 shows a nucleotide sequence (SEQ ID NO:98) designated herein as DNA34508.

Figure 99 shows a nucleotide sequence (SEQ ID NO:99) designated herein as DNA34807.

Figure 100 shows a nucleotide sequence (SEQ ID NO:100) designated herein as DNA34832.

Figure 101 shows a nucleotide sequence (SEQ ID NO:101) designated herein as DNA36223.

Figure 102 shows a nucleotide sequence (SEQ ID NO:102) designated herein as DNA36240.

Figure 103 shows a nucleotide sequence (SEQ ID NO:103) designated herein as DNA36490.

Figure 104 shows a nucleotide sequence (SEQ ID NO:104) designated herein as DNA36516.

Figure 105 shows a nucleotide sequence (SEQ ID NO:105) designated herein as DNA36533.

Figure 106 shows a nucleotide sequence (SEQ ID NO:106) designated herein as DNA36538.

Figure 107 shows a nucleotide sequence (SEQ ID NO:107) designated herein as DNA36788.

Figure 108 shows a nucleotide sequence (SEQ ID NO:108) designated herein as DNA36818.

Figure 109 shows a nucleotide sequence (SEQ ID NO:109) designated herein as DNA36868.

Figure 110 shows a nucleotide sequence (SEQ ID NO:110) designated herein as DNA37393.

Figure 111 shows a nucleotide sequence (SEQ ID NO:111) designated herein as DNA27588.

Figure 112 shows a nucleotide sequence (SEQ ID NO:112) designated herein as DNA37602.

Figure 113 shows a nucleotide sequence (SEQ ID NO:113) designated herein as DNA37642.

Figure 114 shows a nucleotide sequence (SEQ ID NO:114) designated herein as DNA37676.

Figure 115 shows a nucleotide sequence (SEQ ID NO:115) designated herein as DNA37721.

Figure 116 shows a nucleotide sequence (SEQ ID NO:116) designated herein as DNA37759.

Figure 117 shows a nucleotide sequence (SEQ ID NO:117) designated herein as DNA37857.

Figure 118 shows a nucleotide sequence (SEQ ID NO:118) designated herein as DNA37937.

Figure 119 shows a nucleotide sequence (SEQ ID NO:119) designated herein as DNA38037.

Figure 120 shows a nucleotide sequence (SEQ ID NO:120) designated herein as DNA38050.

Figure 121 shows a nucleotide sequence (SEQ ID NO:121) designated herein as DNA38053.

Figure 122 shows a nucleotide sequence (SEQ ID NO:122) designated herein as DNA38312.

Figure 123 shows a nucleotide sequence (SEQ ID NO:123) designated herein as DNA38360.

Figure 124 shows a nucleotide sequence (SEQ ID NO:124) designated herein as DNA38600.

Figure 125 shows a nucleotide sequence (SEQ ID NO:125) designated herein as DNA38720.

Figure 126 shows a nucleotide sequence (SEQ ID NO:126) designated herein as DNA38727.

Figure 127 shows a nucleotide sequence (SEQ ID NO:127) designated herein as DNA38731.

Figure 128 shows a nucleotide sequence (SEQ ID NO:128) designated herein as DNA38810.

Figure 129 shows a nucleotide sequence (SEQ ID NO:129) designated herein as DNA38814.

Figure 130 shows a nucleotide sequence (SEQ ID NO:130) designated herein as DNA39378.

Figure 131 shows a nucleotide sequence (SEQ ID NO:131) designated herein as DNA40050.

Figure 132 shows a nucleotide sequence (SEQ ID NO:132) designated herein as DNA40375.

Figure 133 shows a nucleotide sequence (SEQ ID NO:133) designated herein as DNA40382.

Figure 134 shows a nucleotide sequence (SEQ ID NO:134) designated herein as DNA40394.

Figure 135 shows a nucleotide sequence (SEQ ID NO:135) designated herein as DNA40461.

Figure 136 shows a nucleotide sequence (SEQ ID NO:136) designated herein as DNA40735.

Figure 137 shows a nucleotide sequence (SEQ ID NO:137) designated herein as DNA40736.

Figure 138 shows a nucleotide sequence (SEQ ID NO:138) designated herein as DNA40738.

Figure 139 shows a nucleotide sequence (SEQ ID NO:139) designated herein as DNA40739.

Figure 140 shows a nucleotide sequence (SEQ ID NO:140) designated herein as DNA41144.

Figure 141 shows a nucleotide sequence (SEQ ID NO:141) designated herein as DNA41161.

Figure 142 shows a nucleotide sequence (SEQ ID NO:142) designated herein as DNA41186.

Figure 143 shows a nucleotide sequence (SEQ ID NO:143) designated herein as DNA41250.

Figure 144 shows a nucleotide sequence (SEQ ID NO:144) designated herein as DNA41284.

Figure 145 shows a nucleotide sequence (SEQ ID NO:145) designated herein as DNA41303.

Figure 146 shows a nucleotide sequence (SEQ ID NO:146) designated herein as DNA41326.

Figure 147 shows a nucleotide sequence (SEQ ID NO:147) designated herein as DNA41444.

Figure 148 shows a nucleotide sequence (SEQ ID NO:148) designated herein as DNA41445.

Figure 149 shows a nucleotide sequence (SEQ ID NO:149) designated herein as DNA41452.

Figure 150 shows a nucleotide sequence (SEQ ID NO:150) designated herein as DNA41456.

Figure 151 shows a nucleotide sequence (SEQ ID NO:151) designated herein as DNA41458.

Figure 152 shows a nucleotide sequence (SEQ ID NO:152) designated herein as DNA41462.

Figure 153 shows a nucleotide sequence (SEQ ID NO:153) designated herein as DNA41465.

Figure 154 shows a nucleotide sequence (SEQ ID NO:154) designated herein as DNA41475.

Figure 155 shows a nucleotide sequence (SEQ ID NO:155) designated herein as DNA41514.

Figure 156 shows a nucleotide sequence (SEQ ID NO:156) designated herein as DNA41565.

Figure 157 shows a nucleotide sequence (SEQ ID NO:157) designated herein as DNA41566.

Figure 158 shows a nucleotide sequence (SEQ ID NO:158) designated herein as DNA41626.

Figure 159 shows a nucleotide sequence (SEQ ID NO:159) designated herein as DNA41709.

Figure 160 shows a nucleotide sequence (SEQ ID NO:160) designated herein as DNA41775.

Figure 161 shows a nucleotide sequence (SEQ ID NO:161) designated herein as DNA41784.

Figure 162 shows a nucleotide sequence (SEQ ID NO:162) designated herein as DNA42194.

Figure 163 shows a nucleotide sequence (SEQ ID NO:163) designated herein as DNA42279.

Figure 164 shows a nucleotide sequence (SEQ ID NO:164) designated herein as DNA42314.

Figure 165 shows a nucleotide sequence (SEQ ID NO:165) designated herein as DNA42331.

Figure 166 shows a nucleotide sequence (SEQ ID NO:166) designated herein as DNA42358.

Figure 167 shows a nucleotide sequence (SEQ ID NO:167) designated herein as DNA42858.

Figure 168 shows a nucleotide sequence (SEQ ID NO:168) designated herein as DNA42870.

Figure 169 shows a nucleotide sequence (SEQ ID NO:169) designated herein as DNA42875.

Figure 170 shows a nucleotide sequence (SEQ ID NO:170) designated herein as DNA43197.

Figure 171 shows a nucleotide sequence (SEQ ID NO:171) designated herein as DNA43203.

Figure 172 shows a nucleotide sequence (SEQ ID NO:172) designated herein as DNA43295.

Figure 173 shows a nucleotide sequence (SEQ ID NO:173) designated herein as DNA43301.

Figure 174 shows a nucleotide sequence (SEQ ID NO:174) designated herein as DNA43363.

Figure 175 shows a nucleotide sequence (SEQ ID NO:175) designated herein as DNA43420.

Figure 176 shows a nucleotide sequence (SEQ ID NO:176) designated herein as DNA443479.

Figure 177 shows a nucleotide sequence (SEQ ID NO:177) designated herein as DNA43489.

Figure 178 shows a nucleotide sequence (SEQ ID NO:178) designated herein as DNA43498.

Figure 179 shows a nucleotide sequence (SEQ ID NO:179) designated herein as DNA43509.

Figure 180 shows a nucleotide sequence (SEQ ID NO:180) designated herein as DNA43512.

Figure 181 shows a nucleotide sequence (SEQ ID NO:181) designated herein as DNA43531.

Figure 182 shows a nucleotide sequence (SEQ ID NO:182) designated herein as DNA43546.

Figure 183 shows a nucleotide sequence (SEQ ID NO:183) designated herein as DNA43586.

Figure 184 shows a nucleotide sequence (SEQ ID NO:184) designated herein as DNA43862.

Figure 185 shows a nucleotide sequence (SEQ ID NO:185) designated herein as DNA43887.

Figure 186 shows a nucleotide sequence (SEQ ID NO:186) designated herein as DNA43936.

Figure 187 shows a nucleotide sequence (SEQ ID NO:187) designated herein as DNA43961.

Figure 188 shows a nucleotide sequence (SEQ ID NO:188) designated herein as DNA43971.

Figure 189 shows a nucleotide sequence (SEQ ID NO:189) designated herein as DNA44048.

Figure 190 shows a nucleotide sequence (SEQ ID NO:190) designated herein as DNA44920.

Figure 191 shows a nucleotide sequence (SEQ ID NO:191) designated herein as DNA44922.

Figure 192 shows a nucleotide sequence (SEQ ID NO:192) designated herein as DNA44934.

Figure 193 shows a nucleotide sequence (SEQ ID NO:193) designated herein as DNA44987.

Figure 194 shows a nucleotide sequence (SEQ ID NO:194) designated herein as DNA45014.

Figure 195 shows a nucleotide sequence (SEQ ID NO:195) designated herein as DNA45030.

Figure 196 shows a nucleotide sequence (SEQ ID NO:196) designated herein as DNA45051.

Figure 197 shows a nucleotide sequence (SEQ ID NO:197) designated herein as DNA45064.

Figure 198 shows a nucleotide sequence (SEQ ID NO:198) designated herein as DNA45282.

Figure 199 shows a nucleotide sequence (SEQ ID NO:199) designated herein as DNA45288.

Figure 200 shows a nucleotide sequence (SEQ ID NO:200) designated herein as DNA45300.

Figure 201 shows a nucleotide sequence (SEQ ID NO:201) designated herein as DNA45740.

Figure 202 shows a nucleotide sequence (SEQ ID NO:202) designated herein as DNA45759.

Figure 203 shows a nucleotide sequence (SEQ ID NO:203) designated herein as DNA45784.

Figure 204 shows a nucleotide sequence (SEQ ID NO:204) designated herein as DNA45789.

Figure 205 shows a nucleotide sequence (SEQ ID NO:205) designated herein as DNA45816.

Figure 206 shows a nucleotide sequence (SEQ ID NO:206) designated herein as DNA45944.

Figure 207 shows a nucleotide sequence (SEQ ID NO:207) designated herein as DNA45954.

Figure 208 shows a nucleotide sequence (SEQ ID NO:208) designated herein as DNA45964.

Figure 209 shows a nucleotide sequence (SEQ ID NO:209) designated herein as DNA45993.

Figure 210 shows a nucleotide sequence (SEQ ID NO:210) designated herein as DNA46092.

Figure 211 shows a nucleotide sequence (SEQ ID NO:211) designated herein as DNA46213.

Figure 212 shows a nucleotide sequence (SEQ ID NO:212) designated herein as DNA46215.

Figure 213 shows a nucleotide sequence (SEQ ID NO:213) designated herein as DNA46226.

Figure 214 shows a nucleotide sequence (SEQ ID NO:214) designated herein as DNA46328.

Figure 215 shows a nucleotide sequence (SEQ ID NO:215) designated herein as DNA47580.

Figure 216 shows a nucleotide sequence (SEQ ID NO:216) designated herein as DNA47691.

Figure 217 shows a nucleotide sequence (SEQ ID NO:217) designated herein as DNA47751.

Figure 218 shows a nucleotide sequence (SEQ ID NO:218) designated herein as DNA47835.

Figure 219 shows a nucleotide sequence (SEQ ID NO:219) designated herein as DNA47858.

Figure 220 shows a nucleotide sequence (SEQ ID NO:220) designated herein as DNA47890.

Figure 221 shows a nucleotide sequence (SEQ ID NO:221) designated herein as DNA47930.

Figure 222 shows a nucleotide sequence (SEQ ID NO:222) designated herein as DNA47990.

Figure 223 shows a nucleotide sequence (SEQ ID NO:223) designated herein as DNA48054.

Figure 224 shows a nucleotide sequence (SEQ ID NO:224) designated herein as DNA48124.

Figure 225 shows a nucleotide sequence (SEQ ID NO:225) designated herein as DNA48131.

Figure 226 shows a nucleotide sequence (SEQ ID NO:226) designated herein as DNA48162.

Figure 227 shows a nucleotide sequence (SEQ ID NO:227) designated herein as DNA48209.

Figure 228 shows a nucleotide sequence (SEQ ID NO:228) designated herein as DNA48389.

Figure 229 shows a nucleotide sequence (SEQ ID NO:229) designated herein as DNA48446.

Figure 230 shows a nucleotide sequence (SEQ ID NO:230) designated herein as DNA48466.

Figure 231 shows a nucleotide sequence (SEQ ID NO:231) designated herein as DNA48576.

Figure 232 shows a nucleotide sequence (SEQ ID NO:232) designated herein as DNA48598.

Figure 233 shows a nucleotide sequence (SEQ ID NO:233) designated herein as DNA48666.

Figure 234 shows a nucleotide sequence (SEQ ID NO:234) designated herein as DNA48748.

Figure 235 shows a nucleotide sequence (SEQ ID NO:235) designated herein as DNA48777.

Figure 236 shows a nucleotide sequence (SEQ ID NO:236) designated herein as DNA48830.

Figure 237 shows a nucleotide sequence (SEQ ID NO:237) designated herein as DNA49352.

Figure 238 shows a nucleotide sequence (SEQ ID NO:238) designated herein as DNA49407.

Figure 239 shows a nucleotide sequence (SEQ ID NO:239) designated herein as DNA49448.

Figure 240 shows a nucleotide sequence (SEQ ID NO:240) designated herein as DNA49528.

Figure 241 shows a nucleotide sequence (SEQ ID NO:241) designated herein as DNA49529.

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Figure 244 shows a nucleotide sequence (SEQ ID NO:244) designated herein as DNA49992.

Figure 245 shows a nucleotide sequence (SEQ ID NO:245) designated herein as DNA50307.

Figure 246 shows a nucleotide sequence (SEQ ID NO:246) designated herein as DNA50319.

Figure 247 shows a nucleotide sequence (SEQ ID NO:247) designated herein as DNA50346.

Figure 248 shows a nucleotide sequence (SEQ ID NO:248) designated herein as DNA50354.

Figure 249 shows a nucleotide sequence (SEQ ID NO:249) designated herein as DNA50356.

Figure 250 shows a nucleotide sequence (SEQ ID NO:250) designated herein as DNA50405.

Figure 251 shows a nucleotide sequence (SEQ ID NO:251) designated herein as DNA50421.

Figure 252 shows a nucleotide sequence (SEQ ID NO:252) designated herein as DNA50423.

Figure 253 shows a nucleotide sequence (SEQ ID NO:253) designated herein as DNA50527.

Figure 254 shows a nucleotide sequence (SEQ ID NO:254) designated herein as DNA50584.

Figure 255 shows a nucleotide sequence (SEQ ID NO:255) designated herein as DNA50626.

Figure 256 shows a nucleotide sequence (SEQ ID NO:256) designated herein as DNA50637.

Figure 257 shows a nucleotide sequence (SEQ ID NO:257) designated herein as DNA50650.

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Figure 259 shows a nucleotide sequence (SEQ ID NO:259) designated herein as DNA50675.

Figure 260 shows a nucleotide sequence (SEQ ID NO:260) designated herein as DNA50698.

Figure 261 shows a nucleotide sequence (SEQ ID NO:261) designated herein as DNA50730.

Figure 262 shows a nucleotide sequence (SEQ ID NO:262) designated herein as DNA50737.

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Figure 269 shows a nucleotide sequence (SEQ ID NO:269) designated herein as DNA52199.

Figure 270 shows a nucleotide sequence (SEQ ID NO:270) designated herein as DNA52218.

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Figure 272 shows a nucleotide sequence (SEQ ID NO:272) designated herein as DNA54446.

Figure 273 shows a nucleotide sequence (SEQ ID NO:273) designated herein as DNA54552.

Figure 274 shows a nucleotide sequence (SEQ ID NO:274) designated herein as DNA54580.

Figure 275 shows a nucleotide sequence (SEQ ID NO:275) designated herein as DNA54623.

Figure 276 shows a nucleotide sequence (SEQ ID NO:276) designated herein as DNA54672.

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Figure 278 shows a nucleotide sequence (SEQ ID NO:278) designated herein as DNA54856.

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Figure 283 shows a nucleotide sequence (SEQ ID NO:283) designated herein as DNA55198.

Figure 284 shows a nucleotide sequence (SEQ ID NO:284) designated herein as DNA55199.

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Figure 289 shows a nucleotide sequence (SEQ ID NO:289) designated herein as DNA56556.

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Figure 325 shows a nucleotide sequence (SEQ ID NO:325) designated herein as DNA62261.

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Figure 334 shows a nucleotide sequence (SEQ ID NO:334) designated herein as DNA64101.

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Figure 336 shows a nucleotide sequence (SEQ ID NO:336) designated herein as DNA64193.

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Figure 346 shows a nucleotide sequence (SEQ ID NO:346) designated herein as DNA64569.

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Figure 351 shows a nucleotide sequence (SEQ ID NO:351) designated herein as DNA65644.

Figure 352 shows a nucleotide sequence (SEQ ID NO:352) designated herein as DNA65720.

Figure 353 shows a nucleotide sequence (SEQ ID NO:353) designated herein as DNA65752.

Figure 354 shows a nucleotide sequence (SEQ ID NO:354) designated herein as DNA65771.

Figure 355 shows a nucleotide sequence (SEQ ID NO:355) designated herein as DNA65833.

Figure 356 shows a nucleotide sequence (SEQ ID NO:356) designated herein as DNA65836.

Figure 357 shows a nucleotide sequence (SEQ ID NO:357) designated herein as DNA65864.

Figure 358 shows a nucleotide sequence (SEQ ID NO:358) designated herein as DNA65869.

Figure 359 shows a nucleotide sequence (SEQ ID NO:359) designated herein as DNA65928.

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Figure 361 shows a nucleotide sequence (SEQ ID NO:361) designated herein as DNA66095.

Figure 362 shows a nucleotide sequence (SEQ ID NO:362) designated herein as DNA66197.

Figure 363 shows a nucleotide sequence (SEQ ID NO:363) designated herein as DNA66217.

Figure 364 shows a nucleotide sequence (SEQ ID NO:364) designated herein as DNA66231.

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Figure 368 shows a nucleotide sequence (SEQ ID NO:368) designated herein as DNA68013.

Figure 369 shows a nucleotide sequence (SEQ ID NO:369) designated herein as DNA68018.

Figure 370 shows a nucleotide sequence (SEQ ID NO:370) designated herein as DNA68034.

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Figure 372 shows a nucleotide sequence (SEQ ID NO:372) designated herein as DNA68248.

Figure 373 shows a nucleotide sequence (SEQ ID NO:373) designated herein as DNA68383.

Figure 374 shows a nucleotide sequence (SEQ ID NO:374) designated herein as DNA68423.

Figure 375 shows a nucleotide sequence (SEQ ID NO:375) designated herein as DNA68441.

Figure 376 shows a nucleotide sequence (SEQ ID NO:376) designated herein as DNA68459.

Figure 377 shows a nucleotide sequence (SEQ ID NO:377) designated herein as DNA68509.

Figure 378 shows a nucleotide sequence (SEQ ID NO:378) designated herein as DNA68514.

Figure 379 shows a nucleotide sequence (SEQ ID NO:379) designated herein as DNA68521.

Figure 380 shows a nucleotide sequence (SEQ ID NO:380) designated herein as DNA68532.

Figure 381 shows a nucleotide sequence (SEQ ID NO:381) designated herein as DNA68540.

Figure 382 shows a nucleotide sequence (SEQ ID NO:382) designated herein as DNA68561.

Figure 383 shows a nucleotide sequence (SEQ ID NO:383) designated herein as DNA68585.

Figure 384 shows a nucleotide sequence (SEQ ID NO:384) designated herein as DNA69491.

Figure 385 shows a nucleotide sequence (SEQ ID NO:385) designated herein as DNA70222.

Figure 386 shows a nucleotide sequence (SEQ ID NO:386) designated herein as DNA70239.

Figure 387 shows a nucleotide sequence (SEQ ID NO:387) designated herein as DNA70244.

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Figure 390 shows a nucleotide sequence (SEQ ID NO:390) designated herein as DNA70413.

Figure 391 shows a nucleotide sequence (SEQ ID NO:391) designated herein as DNA70526.

Figure 392 shows a nucleotide sequence (SEQ ID NO:392) designated herein as DNA70685.

Figure 393 shows a nucleotide sequence (SEQ ID NO:393) designated herein as DNA70732.

Figure 394 shows a nucleotide sequence (SEQ ID NO:394) designated herein as DNA72634.

Figure 395 shows a nucleotide sequence (SEQ ID NO:395) designated herein as DNA72683.

Figure 396 shows a nucleotide sequence (SEQ ID NO:396) designated herein as DNA72695.

Figure 397 shows a nucleotide sequence (SEQ ID NO:397) designated herein as DNA72864.

Figure 398 shows a nucleotide sequence (SEQ ID NO:398) designated herein as DNA73156.

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Figure 400 shows a nucleotide sequence (SEQ ID NO:400) designated herein as DNA74052.

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Figure 405 shows a nucleotide sequence (SEQ ID NO:405) designated herein as DNA74218.

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Figure 408 shows a nucleotide sequence (SEQ ID NO:408) designated herein as DNA75062.

Figure 409 shows a nucleotide sequence (SEQ ID NO:409) designated herein as DNA76137.

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Figure 417 shows a nucleotide sequence (SEQ ID NO:417) designated herein as DNA78103.

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Figure 419 shows a nucleotide sequence (SEQ ID NO:419) designated herein as DNA78746.

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Figure 424 shows a nucleotide sequence (SEQ ID NO:424) designated herein as DNA79617.

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Figure 427 shows a nucleotide sequence (SEQ ID NO:427) designated herein as DNA79661.

Figure 428 shows a nucleotide sequence (SEQ ID NO:428) designated herein as DNA79684.

Figure 429 shows a nucleotide sequence (SEQ ID NO:429) designated herein as DNA79717.

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Figure 435 shows a nucleotide sequence (SEQ ID NO:435) designated herein as DNA80615.

Figure 436 shows a nucleotide sequence (SEQ ID NO:436) designated herein as DNA80623.

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Figure 447 shows a nucleotide sequence (SEQ ID NO:447) designated herein as DNA82166.

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Figure 456 shows a nucleotide sequence (SEQ ID NO:456) designated herein as DNA82786.

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Figure 459 shows a nucleotide sequence (SEQ ID NO:459) designated herein as DNA82935.

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Figure 471 shows a nucleotide sequence (SEQ ID NO:471) designated herein as DNA85072.
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Figure 477 shows a nucleotide sequence (SEQ ID NO:477) designated herein as DNA85357.
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Figure 479 shows a nucleotide sequence (SEQ ID NO:479) designated herein as DNA85371.
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Figure 484 shows a nucleotide sequence (SEQ ID NO:484) designated herein as DNA86969.
Figure 485 shows a nucleotide sequence (SEQ ID NO:485) designated herein as DNA87050.
Figure 486 shows a nucleotide sequence (SEQ ID NO:486) designated herein as DNA87094.
Figure 487 shows a nucleotide sequence (SEQ ID NO:487) designated herein as DNA87126.
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Figure 493 shows a nucleotide sequence (SEQ ID NO:493) designated herein as DNA87649.
Figure 494 shows a nucleotide sequence (SEQ ID NO:494) designated herein as DNA89340.
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Figure 496 shows a nucleotide sequence (SEQ ID NO:496) designated herein as DNA89365.
Figure 497 shows a nucleotide sequence (SEQ ID NO:497) designated herein as DNA89419.
Figure 498 shows a nucleotide sequence (SEQ ID NO:498) designated herein as DNA89470.
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Figure 500 shows a nucleotide sequence (SEQ ID NO:500) designated herein as DNA89549.
Figure 501 shows a nucleotide sequence (SEQ ID NO:501) designated herein as DNA89606.
Figure 502 shows a nucleotide sequence (SEQ ID NO:502) designated herein as DNA89615.
Figure 503 shows a nucleotide sequence (SEQ ID NO:503) designated herein as DNA89669.
Figure 504 shows a nucleotide sequence (SEQ ID NO:504) designated herein as DNA89760.
Figure 505 shows a nucleotide sequence (SEQ ID NO:505) designated herein as DNA89766.
Figure 506 shows a nucleotide sequence (SEQ ID NO:506) designated herein as DNA89772.
Figure 507 shows a nucleotide sequence (SEQ ID NO:507) designated herein as DNA89773.
Figure 508 shows a nucleotide sequence (SEQ ID NO:508) designated herein as DNA89774.

Figure 509 shows a nucleotide sequence (SEQ ID NO:509) designated herein as DNA89872.
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Figure 514 shows a nucleotide sequence (SEQ ID NO:514) designated herein as DNA91507.
Figure 515 shows a nucleotide sequence (SEQ ID NO:515) designated herein as DNA93615.
Figure 516 shows a nucleotide sequence (SEQ ID NO:516) designated herein as DNA94011.
Figure 517 shows a nucleotide sequence (SEQ ID NO:517) designated herein as DNA94043.
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Figure 519 shows a nucleotide sequence (SEQ ID NO:519) designated herein as DNA94097.
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Figure 521 shows a nucleotide sequence (SEQ ID NO:521) designated herein as DNA94100.
Figure 522 shows a nucleotide sequence (SEQ ID NO:522) designated herein as DNA94126.
Figure 523 shows a nucleotide sequence (SEQ ID NO:523) designated herein as DNA94136.
Figure 524 shows a nucleotide sequence (SEQ ID NO:524) designated herein as DNA94156.
Figure 525 shows a nucleotide sequence (SEQ ID NO:525) designated herein as DNA94219.
Figure 526 shows a nucleotide sequence (SEQ ID NO:526) designated herein as DNA94254.
Figure 527 shows a nucleotide sequence (SEQ ID NO:527) designated herein as DNA94274.
Figure 528 shows a nucleotide sequence (SEQ ID NO:528) designated herein as DNA94292.
Figure 529 shows a nucleotide sequence (SEQ ID NO:529) designated herein as DNA94360.
Figure 530 shows a nucleotide sequence (SEQ ID NO:530) designated herein as DNA94377.
Figure 531 shows a nucleotide sequence (SEQ ID NO:531) designated herein as DNA94477.
Figure 532 shows a nucleotide sequence (SEQ ID NO:532) designated herein as DNA94518.
Figure 533 shows a nucleotide sequence (SEQ ID NO:533) designated herein as DNA94533.
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Figure 536 shows a nucleotide sequence (SEQ ID NO:536) designated herein as DNA97374.
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Figure 538 shows a nucleotide sequence (SEQ ID NO:538) designated herein as DNA97581.
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Figure 542 shows a nucleotide sequence (SEQ ID NO:542) designated herein as DNA97987.
Figure 543 shows a nucleotide sequence (SEQ ID NO:543) designated herein as DNA97995.
Figure 544 shows a nucleotide sequence (SEQ ID NO:544) designated herein as DNA98293.
Figure 545 shows a nucleotide sequence (SEQ ID NO:545) designated herein as DNA98294.
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Figure 547 shows a nucleotide sequence (SEQ ID NO:547) designated herein as DNA98360.

Figure 548 shows a nucleotide sequence (SEQ ID NO:548) designated herein as DNA98829.

Figure 549 shows a nucleotide sequence (SEQ ID NO:549) designated herein as DNA101514.

Figure 550 shows a nucleotide sequence (SEQ ID NO:550) designated herein as DNA101572.

Figure 551 shows a nucleotide sequence (SEQ ID NO:551) designated herein as DNA101580.

Figure 552 shows a nucleotide sequence (SEQ ID NO:552) designated herein as DNA101595.

Figure 553 shows a nucleotide sequence (SEQ ID NO:553) designated herein as DNA101633.

Figure 554 shows a nucleotide sequence (SEQ ID NO:554) designated herein as DNA101717.

Figure 555 shows a nucleotide sequence (SEQ ID NO:555) designated herein as DNA101768.

Figure 556 shows a nucleotide sequence (SEQ ID NO:556) designated herein as DNA107332.

Figure 557 shows a nucleotide sequence (SEQ ID NO:557) designated herein as DNA43499.

Figure 558 shows a nucleotide sequence (SEQ ID NO:558) designated herein as DNA45713.

Figure 559 shows a nucleotide sequence (SEQ ID NO:559) designated herein as DNA46089.

Figure 560 shows a nucleotide sequence (SEQ ID NO:560) designated herein as DNA68256.

Figure 561 shows a nucleotide sequence (SEQ ID NO:561) designated herein as DNA70305.

Figure 562 shows a nucleotide sequence (SEQ ID NO:562) designated herein as DNA82953.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. Definitions

The term "SRT polypeptide" when used herein encompasses "native sequence SRT polypeptides" and "SRT polypeptide variants" (which are further defined herein). "SRT" is a designation given to those polypeptides which are encoded by the nucleic acid molecules shown in the accompanying figures and variants thereof, nucleic acid molecules comprising the sequence shown in the accompanying figures and variants thereof as well as fragments of the above. The SRT polypeptides of the invention may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant and/or synthetic methods.

A "native sequence" SRT polypeptide comprises a polypeptide having the same amino acid sequence as the corresponding SRT polypeptide derived from nature. Such native sequence SRT polypeptides can be isolated from nature or can be produced by recombinant and/or synthetic means. The term "native sequence SRT polypeptide" specifically encompasses naturally-occurring truncated or secreted forms (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide.

An SRT polypeptide "extracellular domain" or "ECD" refers to a form of the SRT polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, an SRT polypeptide ECD will have less than about 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than about 0.5% of such domains. It will be understood that any transmembrane domain(s) identified for the SRT polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but

most likely by no more than about 5 amino acids at either end of the domain as initially identified.

"Variant SRT polypeptide" means an active SRT polypeptide as defined below having at least about 80% amino acid sequence identity with the amino acid sequence of a specifically derived fragment of any other polypeptide which will be specifically recited. Such variant SRT polypeptides include, for instance, SRT polypeptides wherein one or more amino acid residues are added, or deleted, at the N- and/or C-terminus, as well as within one or more internal domains, of the full-length amino acid sequence. Ordinarily, a variant SRT polypeptide will have at least about 80% amino acid sequence identity, more preferably at least about 81% amino acid sequence identity, more preferably at least about 82% amino acid sequence identity, more preferably at least about 83% amino acid sequence identity, more preferably at least about 84% amino acid sequence identity, more preferably at least about 85% amino acid sequence identity, more preferably at least about 86% amino acid sequence identity, more preferably at least about 87% amino acid sequence identity, more preferably at least about 88% amino acid sequence identity, more preferably at least about 89% amino acid sequence identity, more preferably at least about 90% amino acid sequence identity, more preferably at least about 91% amino acid sequence identity, more preferably at least about 92% amino acid sequence identity, more preferably at least about 93% amino acid sequence identity, more preferably at least about 94% amino acid sequence identity, more preferably at least about 95% amino acid sequence identity, more preferably at least about 96% amino acid sequence identity, more preferably at least about 97% amino acid sequence identity, more preferably at least about 98% amino acid sequence identity and yet more preferably at least about 99% amino acid sequence identity with an SRT polypeptide encoded by a nucleic acid molecule shown in one of the accompanying figures or a specified fragment thereof. SRT variant polypeptides do not encompass the native SRT polypeptide sequence. Ordinarily, SRT variant polypeptides are at least about 10 amino acids in length, often at least about 20 amino acids in length, more often at least about 30 amino acids in length, more often at least about 40 amino acids in length, more often at least about 50 amino acids in length, more often at least about 60 amino acids in length, more often at least about 70 amino acids in length, more often at least about 80 amino acids in length, more often at least about 90 amino acids in length, more often at least about 100 amino acids in length, more often at least about 150 amino acids in length, more often at least about 200 amino acids in length, more often at least about 250 amino acids in length, more often at least about 300 amino acids in length, or more.

"Percent (%) amino acid sequence identity" with respect to the SRT polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in a SRT sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, ALIGN-2 or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full-length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are obtained as described below by using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table

1. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

For purposes herein, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction X/Y

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations, Tables 2 and 3 demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated "Comparison Protein" to the amino acid sequence designated "PRO".

Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described above using the ALIGN-2 sequence comparison computer program. However, % amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from http://www.ncbi.nlm.nih.gov. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction X/Y

where X is the number of amino acid residues scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of A and B, and where Y is the total number of amino acid residues

in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A.

"SRT variant polynucleotide" or "SRT variant nucleic acid sequence" means a nucleic acid molecule which has at least about 80% nucleic acid sequence identity with any of the nucleic acid sequences shown in the accompanying figures or a specified fragment thereof. Ordinarily, a SRT variant polynucleotide will have at least about 80% nucleic acid sequence identity, more preferably at least about 81% nucleic acid sequence identity, more preferably at least about 82% nucleic acid sequence identity, more preferably at least about 83% nucleic acid sequence identity, more preferably at least about 84% nucleic acid sequence identity, more preferably at least about 85% nucleic acid sequence identity, more preferably at least about 86% nucleic acid sequence identity, more preferably at least about 87% nucleic acid sequence identity, more preferably at least about 88% nucleic acid sequence identity, more preferably at least about 89% nucleic acid sequence identity, more preferably at least about 90% nucleic acid sequence identity, more preferably at least about 91% nucleic acid sequence identity, more preferably at least about 92% nucleic acid sequence identity, more preferably at least about 93% nucleic acid sequence identity, more preferably at least about 94% nucleic acid sequence identity, more preferably at least about 95% nucleic acid sequence identity, more preferably at least about 96% nucleic acid sequence identity, more preferably at least about 97% nucleic acid sequence identity, more preferably at least about 98% nucleic acid sequence identity and yet more preferably at least about 99% nucleic acid sequence identity with any of the nucleic acid sequences shown in the accompanying figures or a specified fragment thereof. SRT polynucleotide variants do not encompass the native SRT nucleotide sequence.

Ordinarily, SRT variant polynucleotides are at least about 10 nucleotides in length, often at least about 15 nucleotides in length, often at least about 20 nucleotides in length, often at least about 25 nucleotides in length, often at least about 30 nucleotides in length, often at least about 35 nucleotides in length, often at least about 40 nucleotides in length, often at least about 45 nucleotides in length, often at least about 50 nucleotides in length, often at least about 55 nucleotides in length, often at least about 60 nucleotides in length, often at least about 65 nucleotides in length, often at least about 65 nucleotides in length, often at least about 70 nucleotides in length, often at least about 75 nucleotides in length, often at least about 80 nucleotides in length, often at least about 85 nucleotides in length, often at least about 90 nucleotides in length, often at least about 95 nucleotides in length, often at least about 100 nucleotides in length, or more.

"Percent (%) nucleic acid sequence identity" with respect to the SRT polypeptide-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in a SRT polypeptide-encoding nucleic acid sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, ALIGN-2 or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full-length of the sequences being compared. For purposes herein, however, % nucleic acid sequence identity values are obtained as

described below by using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

For purposes herein, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

100 times the fraction W/Z

where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C. As examples of % nucleic acid sequence identity calculations, Tables 4 and 5 demonstrate how to calculate the % nucleic acid sequence identity of the nucleic acid sequence designated "Comparison DNA" to the nucleic acid sequence designated "PRO-DNA".

Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described above using the ALIGN-2 sequence comparison computer program. However, % nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from http://www.ncbi.nlm.nih.gov. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

100 times the fraction W/Z

where W is the number of nucleotides scored as identical matches by the sequence alignment program NCBI-

BLAST2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C.

In other embodiments, SRT variant polynucleotides are nucleic acid molecules that encode an active SRT polypeptide and which are capable of hybridizing, preferably under stringent hybridization conditions, to any of the nucleotide sequences shown in the accompanying figures or their complements. SRT variant polypeptides may be those that are encoded by a SRT variant polynucleotide.

The term "positives", in the context of the amino acid sequence identity comparisons performed as described above, includes amino acid residues in the sequences compared that are not only identical, but also those that have similar properties. Amino acid residues that score a positive value to an amino acid residue of interest are those that are either identical to the amino acid residue of interest or are a preferred substitution (as defined in Table 6 below) of the amino acid residue of interest.

For purposes herein, the % value of positives of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % positives to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction X/Y

where X is the number of amino acid residues scoring a positive value as defined above by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % positives of A to B will not equal the % positives of B to A.

"Isolated," when used to describe the various polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Preferably, the isolated polypeptide is free of association with all components with which it is naturally associated. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of the SRT natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

An "isolated" nucleic acid molecule encoding a SRT polypeptide is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the SRT-encoding nucleic acid. Preferably, the isolated nucleic is free of association with all components with which it is naturally associated. An isolated SRT-encoding nucleic acid molecule is

other than in the form or setting in which it is found in nature. Isolated nucleic acid molecules therefore are distinguished from the SRT-encoding nucleic acid molecule as it exists in natural cells. However, an isolated nucleic acid molecule encoding a SRT polypeptide includes SRT-encoding nucleic acid molecules contained in cells that ordinarily express SRT where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

The term "antibody" is used in the broadest sense and specifically covers, for example, single anti-SRT monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies), anti-SRT antibody compositions with polyepitopic specificity, single chain anti-SRT antibodies, and fragments of anti-SRT antibodies (see below). The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel *et al.*, Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

"Stringent conditions" or "high stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum

albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 μg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately stringent conditions" may be identified as described by Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent that those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

The term "epitope tagged" when used herein refers to a chimeric polypeptide comprising a SRT polypeptide fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

"Active" or "activity" for the purposes herein refers to form(s) of SRT which retain a biological and/or an immunological activity of native or naturally-occurring SRT, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring SRT other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring SRT and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring SRT.

The term "antagonist" is used in the broadest sense, and includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of a native SRT polypeptide disclosed herein. In a similar

manner, the term "agonist" is used in the broadest sense and includes any molecule that mimics a biological activity of a native SRT polypeptide disclosed herein. Suitable agonist or antagonist molecules specifically include agonist or antagonist antibodies or antibody fragments, fragments or amino acid sequence variants of native SRT polypeptides, peptides, small organic molecules, etc. Methods for identifying agonists or antagonists of a SRT polypeptide may comprise contacting a SRT polypeptide with a candidate agonist or antagonist molecule and measuring a detectable change in one or more biological activities normally associated with the SRT polypeptide.

"Treatment" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

"Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. "Intermittent" administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature.

"Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Preferably, the mammal is human.

Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

"Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, polyethylene glycol (PEG), and PLURONICS™.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies (Zapata et al., Protein Eng. 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. Pepsin treatment yields an $F(ab')_2$ fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the VH-VL dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab fragments differ from Fab' fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2.

"Single-chain Fv" or "sFv" antibody fragments comprise the VH and VL domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the VH and VL domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (VH) connected to a light-chain variable domain (VL) in the same polypeptide chain (VH - VL). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993).

An "isolated" antibody is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or

nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

The word "label" when used herein refers to a detectable compound or composition which is conjugated directly or indirectly to the antibody so as to generate a "labeled" antibody. The label may be detectable by itself (e.g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable.

By "solid phase" is meant a non-aqueous matrix to which the antibody of the present invention can adhere. Examples of solid phases encompassed herein include those formed partially or entirely of glass (e.g., controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (e.g., an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No. 4,275,149.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as a SRT polypeptide or antibody thereto) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

A "small molecule" is defined herein to have a molecular weight below about 500 Daltons.

An "oligonucleotide" or "oligomer" is a stretch of nucleotide residues which has a sufficient number of bases to be used in a polymerase chain reaction (PCR). These sequences are based on (or designed from) genomic or cDNA sequences and may be used to amplify, confirm, or reveal the presence of an identical, similar or complementary DNA or RNA in a particular cell or tissue. Oligonucleotides or oligomers comprise portions of a DNA sequence having at least about 10 nucleotides as described above. Oligonucleotides may be chemically synthesized and may be used as probes.

"Probes" are nucleic acid sequences of variable length, preferably between about 10 and as many as about 6000 nucleotides, depending upon use. They are used in the detection of identical, similar or complementary nucleic acid sequences. Longer length probes are usually obtained from a natural or recombinant source, are highly specific and are often much slower to hybridize to a target nucleic acid than are oligomers. Probes may be single- or double-stranded and may be carefully designaed to have specificity in PCR, hybridization membrane-based, or ELISA-like technologies.

"Detectably labeled" with regard to a nucleic acid molecule of the present invention means that the molecule has attached thereto, either covalently or non-covalently, a compound which is detectable such as, for example, radionuclides, enzymes, fluorescent, chemi-luminescent, or chromogenic agents. Detectable labels associate with, establish the presence of, and may allow quantification of a particular nucleic or amino acid sequence.

A "portion" or "fragment" of a polynucleotide or nucleic acid molecule comprises all or any part of the nucleotide sequence having fewer nucleotides than about 6 kb, preferably fewer than about 1 kb which can be used as a probe. Such probes may be labelled with detectable labels using nick translation, Klenow fill-in reaction, PCR or other methods well known in the art. After pretesting to optimize reaction conditions and to eliminate false positives, nucleic acid probes may be used in Southern, Northern or in situ hybridizations to determine whether DNA or RNA encoding the protein is present in a biological sample, cell type, tissue, organ or organism.

Table 1

```
/*
 *
 * C-C increased from 12 to 15
 * Z is average of EQ
 * B is average of ND
 * match with stop is _M; stop-stop = 0; J (joker) match = 0
 */
#define   _M      -8       /* value of a match with a stop */

int       _day[26][26] = {
/*       A B C D E F G H I J K L M N O P Q R S T U V W X Y Z */
/* A */   { 2, 0,-2, 0, 0,-4, 1,-1,-1, 0,-1,-2,-1, 0,_M, 1, 0,-2, 1, 1, 0, 0,-6, 0,-3, 0},
/* B */   { 0, 3,-4, 3, 2,-5, 0, 1,-2, 0, 0,-3,-2, 2,_M,-1, 1, 0, 0, 0, 0,-2,-5, 0,-3, 1},
/* C */   {-2,-4,15,-5,-5,-4,-3,-3,-2, 0,-5,-6,-5,-4,_M,-3,-5,-4, 0,-2, 0,-2,-8, 0, 0,-5},
/* D */   { 0, 3,-5, 4, 3,-6, 1, 1,-2, 0, 0,-4,-3, 2,_M,-1, 2,-1, 0, 0, 0,-2,-7, 0,-4, 2},
/* E */   { 0, 2,-5, 3, 4,-5, 0, 1,-2, 0, 0,-3,-2, 1,_M,-1, 2,-1, 0, 0, 0,-2,-7, 0,-4, 3},
/* F */   {-4,-5,-4,-6,-5, 9,-5,-2, 1, 0,-5, 2, 0,-4,_M,-5,-5,-4,-3,-3, 0,-1, 0, 0, 7,-5},
/* G */   { 1, 0,-3, 1, 0,-5, 5,-2,-3, 0,-2,-4,-3, 0,_M,-1,-1,-3, 1, 0, 0,-1,-7, 0,-5, 0},
/* H */   {-1, 1,-3, 1, 1,-2,-2, 6,-2, 0, 0,-2,-2, 2,_M, 0, 3, 2,-1,-1, 0,-2,-3, 0, 0, 2},
/* I */   {-1,-2,-2,-2,-2, 1,-3,-2, 5, 0,-2, 2, 2,-2,_M,-2,-2,-2,-1, 0, 0, 4,-5, 0,-1,-2},
/* J */   { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,_M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* K */   {-1, 0,-5, 0, 0,-5,-2, 0,-2, 0, 5,-3, 0, 1,_M,-1, 1, 3, 0, 0, 0,-2,-3, 0,-4, 0},
/* L */   {-2,-3,-6,-4,-3, 2,-4,-2, 2, 0,-3, 6, 4,-3,_M,-3,-2,-3,-3,-1, 0, 2,-2, 0,-1,-2},
/* M */   {-1,-2,-5,-3,-2, 0,-3,-2, 2, 0, 0, 4, 6,-2,_M,-2,-1, 0,-2,-1, 0, 2,-4, 0,-2,-1},
/* N */   { 0, 2,-4, 2, 1,-4, 0, 2,-2, 0, 1,-3,-2, 2,_M,-1, 1, 0, 1, 0, 0,-2,-4, 0,-2, 1},
/* O */   {_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M, 0,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M},
/* P */   { 1,-1,-3,-1,-1,-5,-1, 0,-2, 0,-1,-3,-2,-1,_M, 6, 0, 0, 1, 0, 0,-1,-6, 0,-5, 0},
/* Q */   { 0, 1,-5, 2, 2,-5,-1, 3,-2, 0, 1,-2,-1, 1,_M, 0, 4, 1,-1,-1, 0,-2,-5, 0,-4, 3},
/* R */   {-2, 0,-4,-1,-1,-4,-3, 2,-2, 0, 3,-3, 0, 0,_M, 0, 1, 6, 0,-1, 0,-2, 2, 0,-4, 0},
/* S */   { 1, 0, 0, 0, 0,-3, 1,-1,-1, 0, 0,-3,-2, 1,_M, 1,-1, 0, 2, 1, 0,-1,-2, 0,-3, 0},
/* T */   { 1, 0,-2, 0, 0,-3, 0,-1, 0, 0, 0,-1,-1, 0,_M, 0,-1,-1, 1, 3, 0, 0,-5, 0,-3, 0},
/* U */   { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,_M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* V */   { 0,-2,-2,-2,-2,-1,-1,-2, 4, 0,-2, 2, 2,-2,_M,-1,-2,-2,-1, 0, 0, 4,-6, 0,-2,-2},
/* W */   {-6,-5,-8,-7,-7, 0,-7,-3,-5, 0,-3,-2,-4,-4,_M,-6,-5, 2,-2,-5, 0,-6,17, 0, 0,-6},
/* X */   { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,_M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* Y */   {-3,-3, 0,-4,-4, 7,-5, 0,-1, 0,-4,-1,-2,-2,_M,-5,-4,-4,-3,-3, 0,-2, 0, 0,10,-4},
/* Z */   { 0, 1,-5, 2, 3,-5, 0, 2,-2, 0, 0,-2,-1, 1,_M, 0, 3, 0, 0, 0, 0,-2,-6, 0,-4, 4}
};
```


Table 1 (cont')

```
/*
 */
#include <stdio.h>
#include <ctype.h>

#define  MAXJMP      16      /* max jumps in a diag */
#define  MAXGAP      24      /* don't continue to penalize gaps larger than this */
#define  JMPS        1024    /* max jmps in an path */
#define  MX          4       /* save if there's at least MX-1 bases since last jmp */

#define  DMAT        3       /* value of matching bases */
#define  DMIS        0       /* penalty for mismatched bases */
#define  DINS0       8       /* penalty for a gap */
#define  DINS1       1       /* penalty per base */
#define  PINS0       8       /* penalty for a gap */
#define  PINS1       4       /* penalty per residue */

struct jmp {
        short           n[MAXJMP];      /* size of jmp (neg for dely) */
        unsigned short  x[MAXJMP];      /* base no. of jmp in seq x */
};                                      /* limits seq to 2^16 -1 */

struct diag {
        int             score;          /* score at last jmp */
        long            offset;         /* offset of prev block */
        short           ijmp;           /* current jmp index */
        struct jmp      jp;             /* list of jmps */
};

struct path {
        int     spc;            /* number of leading spaces */
        short   n[JMPS];        /* size of jmp (gap) */
        int     x[JMPS];        /* loc of jmp (last elem before gap) */
};

char            *ofile;                 /* output file name */
char            *namex[2];              /* seq names: getseqs() */
char            *prog;                  /* prog name for err msgs */
char            *seqx[2];                       /* seqs: getseqs() */
int             dmax;                   /* best diag: nw() */
int             dmax0;                  /* final diag */
int             dna;                    /* set if dna: main() */
int             endgaps;                /* set if penalizing end gaps */
int             gapx, gapy;             /* total gaps in seqs */
int             len0, len1;             /* seq lens */
int             ngapx, ngapy;           /* total size of gaps */
int             smax;                   /* max score: nw() */
int             *xbm;                   /* bitmap for matching */
long            offset;                 /* current offset in jmp file */
struct  diag    *dx;                    /* holds diagonals */
struct  path    pp[2];                  /* holds path for seqs */

char            *calloc(), *malloc(), *index(), *strcpy();
char            *getseq(), *g_calloc();
```

Table 1 (cont')

```
/* Needleman-Wunsch alignment program
 *
 * usage: progs file1 file2
 *   where file1 and file2 are two dna or two protein sequences.
 *   The sequences can be in upper- or lower-case an may contain ambiguity
 *   Any lines beginning with ';', '>' or '<' are ignored
 *   Max file length is 65535 (limited by unsigned short x in the jmp struct)
 *   A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
 *   Output is in the file "align.out"
 *
 * The program may create a tmp file in /tmp to hold info about traceback.
 * Original version developed under BSD 4.3 on a vax 8650
 */
#include "nw.h"
#include "day.h"

static	_dbval[26] = {
	1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
};

static	_pbval[26] = {
	1, 2|(1<<('D'-'A'))|(1<<('N'-'A')), 4, 8, 16, 32, 64,
	128, 256, 0xFFFFFFF, 1<<10, 1<<11, 1<<12, 1<<13, 1<<14,
	1<<15, 1<<16, 1<<17, 1<<18, 1<<19, 1<<20, 1<<21, 1<<22,
	1<<23, 1<<24, 1<<25|(1<<('E'-'A'))|(1<<('Q'-'A'))
};

main(ac, av)                                                          main
	int	ac;
	char	*av[];
{
	prog = av[0];
	if (ac != 3) {
		fprintf(stderr,"usage: %s file1 file2\n", prog);
		fprintf(stderr,"where file1 and file2 are two dna or two protein sequences.\n");
		fprintf(stderr,"The sequences can be in upper- or lower-case\n");
		fprintf(stderr,"Any lines beginning with ';' or '<' are ignored\n");
		fprintf(stderr,"Output is in the file \"align.out\"\n");
		exit(1);
	}
	namex[0] = av[1];
	namex[1] = av[2];
	seqx[0] = getseq(namex[0], &len0);
	seqx[1] = getseq(namex[1], &len1);
	xbm = (dna)? _dbval : _pbval;

	endgaps = 0;			/* 1 to penalize endgaps */
	ofile = "align.out";		/* output file */

	nw();		/* fill in the matrix, get the possible jmps */
	readjmps();	/* get the actual jmps */
	print();	/* print stats, alignment */

	cleanup(0);	/* unlink any tmp files */
}
```

Table 1 (cont')

```
/* do the alignment, return best score: main()
 * dna: values in Fitch and Smith, PNAS, 80, 1382-1386, 1983
 * pro: PAM 250 values
 * When scores are equal, we prefer mismatches to any gap, prefer
 * a new gap to extending an ongoing gap, and prefer a gap in seqx
 * to a gap in seq y.
 */
nw()                                                                    nw
{
        char            *px, *py;           /* seqs and ptrs */
        int             *ndely, *dely;      /* keep track of dely */
        int             ndelx, delx;        /* keep track of delx */
        int             *tmp;               /* for swapping row0, row1 */
        int             mis;                /* score for each type */
        int             ins0, ins1;         /* insertion penalties */
        register        id;                 /* diagonal index */
        register        ij;                 /* jmp index */
        register        *col0, *col1;       /* score for curr, last row */
        register        xx, yy;             /* index into seqs */

        dx = (struct diag *)g_calloc("to get diags", len0+len1+1, sizeof(struct diag));

        ndely = (int *)g_calloc("to get ndely", len1+1, sizeof(int));
        dely = (int *)g_calloc("to get dely", len1+1, sizeof(int));
        col0 = (int *)g_calloc("to get col0", len1+1, sizeof(int));
        col1 = (int *)g_calloc("to get col1", len1+1, sizeof(int));
        ins0 = (dna)? DINS0 : PINS0;
        ins1 = (dna)? DINS1 : PINS1;

        smax = -10000;
        if (endgaps) {
                for (col0[0] = dely[0] = -ins0, yy = 1; yy <= len1; yy++) {
                        col0[yy] = dely[yy] = col0[yy-1] - ins1;
                        ndely[yy] = yy;
                }
                col0[0] = 0;        /* Waterman Bull Math Biol 84 */
        }
        else
                for (yy = 1; yy <= len1; yy++)
                        dely[yy] = -ins0;

        /* fill in match matrix
         */
        for (px = seqx[0], xx = 1; xx <= len0; px++, xx++) {
                /* initialize first entry in col
                 */
                if (endgaps) {
                        if (xx == 1)
                                col1[0] = delx = -(ins0+ins1);
                        else
                                col1[0] = delx = col0[0] - ins1;
                        ndelx = xx;
                }
                else {
                        col1[0] = 0;
                        delx = -ins0;
                        ndelx = 0;
                }
```


Table 1 (cont')

...nw

```
for (py = seqx[1], yy = 1; yy <= len1; py++, yy++) {
        mis = col0[yy-1];
        if (dna)
                mis += (xbm[*px-'A']&xbm[*py-'A'])? DMAT : DMIS;
        else
                mis += _day[*px-'A'][*py-'A'];

        /* update penalty for del in x seq;
         * favor new del over ongong del
         * ignore MAXGAP if weighting endgaps
         */
        if (endgaps || ndely[yy] < MAXGAP) {
                if (col0[yy] - ins0 >= dely[yy]) {
                        dely[yy] = col0[yy] - (ins0+ins1);
                        ndely[yy] = 1;
                } else {
                        dely[yy] -= ins1;
                        ndely[yy]++;
                }
        } else {
                if (col0[yy] - (ins0+ins1) >= dely[yy]) {
                        dely[yy] = col0[yy] - (ins0+ins1);
                        ndely[yy] = 1;
                } else
                        ndely[yy]++;
        }

        /* update penalty for del in y seq;
         * favor new del over ongong del
         */
        if (endgaps || ndelx < MAXGAP) {
                if (col1[yy-1] - ins0 >= delx) {
                        delx = col1[yy-1] - (ins0+ins1);
                        ndelx = 1;
                } else {
                        delx -= ins1;
                        ndelx++;
                }
        } else {
                if (col1[yy-1] - (ins0+ins1) >= delx) {
                        delx = col1[yy-1] - (ins0+ins1);
                        ndelx = 1;
                } else
                        ndelx++;
        }

        /* pick the maximum score; we're favoring
         * mis over any del and delx over dely
         */
```

Table 1 (cont')

...nw

```
id = xx - yy + len1 - 1;
if (mis >= delx && mis >= dely[yy])
        col1[yy] = mis;
else if (delx >= dely[yy]) {
        col1[yy] = delx;
        ij = dx[id].ijmp;
        if (dx[id].jp.n[0] && (!dna || (ndelx >= MAXJMP
        && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
                dx[id].ijmp++;
                if (++ij >= MAXJMP) {
                        writejmps(id);
                        ij = dx[id].ijmp = 0;
                        dx[id].offset = offset;
                        offset += sizeof(struct jmp) + sizeof(offset);
                }
        }
        dx[id].jp.n[ij] = ndelx;
        dx[id].jp.x[ij] = xx;
        dx[id].score = delx;
}
else {
        col1[yy] = dely[yy];
        ij = dx[id].ijmp;
if (dx[id].jp.n[0] && (!dna || (ndely[yy] >= MAXJMP
        && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
                dx[id].ijmp++;
                if (++ij >= MAXJMP) {
                        writejmps(id);
                        ij = dx[id].ijmp = 0;
                        dx[id].offset = offset;
                        offset += sizeof(struct jmp) + sizeof(offset);
                }
        }
        dx[id].jp.n[ij] = -ndely[yy];
        dx[id].jp.x[ij] = xx;
        dx[id].score = dely[yy];
}
if (xx == len0 && yy < len1) {
        /* last col
         */
        if (endgaps)
                col1[yy] -= ins0+ins1*(len1-yy);
        if (col1[yy] > smax) {
                smax = col1[yy];
                dmax = id;
        }
}
        }
        if (endgaps && xx < len0)
                col1[yy-1] -= ins0+ins1*(len0-xx);
        if (col1[yy-1] > smax) {
                smax = col1[yy-1];
                dmax = id;
        }
        tmp = col0; col0 = col1; col1 = tmp;
}
(void) free((char *)ndely);
(void) free((char *)dely);
(void) free((char *)col0);
(void) free((char *)col1);                    }
```


Table 1 (cont')

```
/*
 *
 * print() -- only routine visible outside this module
 *
 * static:
 * getmat() -- trace back best path, count matches: print()
 * pr_align() -- print alignment of described in array p[]: print()
 * dumpblock() -- dump a block of lines with numbers, stars: pr_align()
 * nums() -- put out a number line: dumpblock()
 * putline() -- put out a line (name, [num], seq, [num]): dumpblock()
 * stars() - -put a line of stars: dumpblock()
 * stripname() -- strip any path and prefix from a seqname
 */

#include "nw.h"

#define SPC     3
#define P_LINE  256     /* maximum output line */
#define P_SPC   3       /* space between name or num and seq */

extern  _day[26][26];
int     olen;           /* set output line length */
FILE    *fx;            /* output file */

print()                                                          print
{
        int     lx, ly, firstgap, lastgap;      /* overlap */

        if ((fx = fopen(ofile, "w")) == 0) {
                fprintf(stderr,"%s: can't write %s\n", prog, ofile);
                cleanup(1);
        }
        fprintf(fx, "<first sequence: %s (length = %d)\n", namex[0], len0);
        fprintf(fx, "<second sequence: %s (length = %d)\n", namex[1], len1);
        olen = 60;
        lx = len0;
        ly = len1;
        firstgap = lastgap = 0;
        if (dmax < len1 - 1) {          /* leading gap in x */
                pp[0].spc = firstgap = len1 - dmax - 1;
                ly -= pp[0].spc;
        }
        else if (dmax > len1 - 1) {   /* leading gap in y */
                pp[1].spc = firstgap = dmax - (len1 - 1);
                lx -= pp[1].spc;
        }
        if (dmax0 < len0 - 1) {         /* trailing gap in x */
                lastgap = len0 - dmax0 -1;
                lx -= lastgap;
        }
        else if (dmax0 > len0 - 1) { /* trailing gap in y */
                lastgap = dmax0 - (len0 - 1);
                ly -= lastgap;
        }
        getmat(lx, ly, firstgap, lastgap);
        pr_align();
}
```

Table 1 (cont')

```
/*
 * trace back the best path, count matches
 */
static
getmat(lx, ly, firstgap, lastgap)                                   getmat
        int     lx, ly;                 /* "core" (minus endgaps) */
        int     firstgap, lastgap;      /* leading trailing overlap */
{
        int             nm, i0, i1, siz0, siz1;
        char            outx[32];
        double          pct;
        register        n0, n1;
        register char   *p0, *p1;

        /* get total matches, score
         */
        i0 = i1 = siz0 = siz1 = 0;
        p0 = seqx[0] + pp[1].spc;
        p1 = seqx[1] + pp[0].spc;
        n0 = pp[1].spc + 1;
        n1 = pp[0].spc + 1;

        nm = 0;
        while ( *p0 && *p1 ) {
                if (siz0) {
                        p1++;
                        n1++;
                        siz0--;
                }
                else if (siz1) {
                        p0++;
                        n0++;
                        siz1--;
                }
                else {
                        if (xbm[*p0-'A']&xbm[*p1-'A'])
                                nm++;
                        if (n0++ == pp[0].x[i0])
                                siz0 = pp[0].n[i0++];
                        if (n1++ == pp[1].x[i1])
                                siz1 = pp[1].n[i1++];
                        p0++;
                        p1++;
                }
        }

        /* pct homology:
         * if penalizing endgaps, base is the shorter seq
         * else, knock off overhangs and take shorter core
         */
        if (endgaps)
                lx = (len0 < len1)? len0 : len1;
        else
                lx = (lx < ly)? lx : ly;
        pct = 100.*(double)nm/(double)lx;
        fprintf(fx, "\n");
        fprintf(fx, "<%d match%s in an overlap of %d: %.2f percent similarity\n",
                nm, (nm == 1)? "" : "es", lx, pct);
```


Table 1 (cont')

...getmat

```
	fprintf(fx, "<gaps in first sequence: %d", gapx);
	if (gapx) {
		(void) sprintf(outx, " (%d %s%s)",
			ngapx, (dna)? "base":"residue", (ngapx == 1)? "":"s");
		fprintf(fx,"%s", outx);

	fprintf(fx, ", gaps in second sequence: %d", gapy);
	if (gapy) {
		(void) sprintf(outx, " (%d %s%s)",
			ngapy, (dna)? "base":"residue", (ngapy == 1)? "":"s");
		fprintf(fx,"%s", outx);
	}
	if (dna)
		fprintf(fx,
		"\n<score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per base)\n",
		smax, DMAT, DMIS, DINS0, DINS1);
	else
		fprintf(fx,
		"\n<score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
		smax, PINS0, PINS1);
	if (endgaps)
		fprintf(fx,
		"<endgaps penalized. left endgap: %d %s%s, right endgap: %d %s%s\n",
		firstgap, (dna)? "base" : "residue", (firstgap == 1)? "" : "s",
		lastgap, (dna)? "base" : "residue", (lastgap == 1)? "" : "s");
	else
		fprintf(fx, "<endgaps not penalized\n");
}

static		nm;		/* matches in core -- for checking */
static		lmax;		/* lengths of stripped file names */
static		ij[2];		/* jmp index for a path */
static		nc[2];		/* number at start of current line */
static		ni[2];		/* current elem number -- for gapping */
static		siz[2];
static char	*ps[2];		/* ptr to current element */
static char	*po[2];		/* ptr to next output char slot */
static char	out[2][P_LINE];	/* output line */
static char	star[P_LINE];	/* set by stars() */

/*
 * print alignment of described in struct path pp[]
 */
static
pr_align()
{
	int		nn;	/* char count */
	int		more;
	register	i;

	for (i = 0, lmax = 0; i < 2; i++) {
		nn = stripname(namex[i]);
		if (nn > lmax)
			lmax = nn;

		nc[i] = 1;
		ni[i] = 1;
		siz[i] = ij[i] = 0;
		ps[i] = seqx[i];
		po[i] = out[i];		}
```

pr_align

Table 1 (cont')

...pr_align

```
	for (nn = nm = 0, more = 1; more; ) {
		for (i = more = 0; i < 2; i++) {
			/*
			 * do we have more of this sequence?
			 */
			if (!*ps[i])
				continue;

			more++;

			if (pp[i].spc) {	/* leading space */
				*po[i]++ = ' ';
				pp[i].spc--;
			}
			else if (siz[i]) {	/* in a gap */
				*po[i]++ = '-';
				siz[i]--;
			}
			else {		/* we're putting a seq element
					 */
				*po[i] = *ps[i];
				if (islower(*ps[i]))
					*ps[i] = toupper(*ps[i]);
				po[i]++;
				ps[i]++;

				/*
				 * are we at next gap for this seq?
				 */
				if (ni[i] == pp[i].x[ij[i]]) {
					/*
					 * we need to merge all gaps
					 * at this location
					 */
					siz[i] = pp[i].n[ij[i]++];
					while (ni[i] == pp[i].x[ij[i]])
						siz[i] += pp[i].n[ij[i]++];
				}
				ni[i]++;
			}
		}
		if (++nn == olen || !more && nn) {
			dumpblock();
			for (i = 0; i < 2; i++)
				po[i] = out[i];
			nn = 0;
		}
	}
}

/*
 * dump a block of lines, including numbers, stars: pr_align()
 */
static
dumpblock()
{
	register i;

	for (i = 0; i < 2; i++)
		*po[i]-- = '\0';
```

dumpblock

Table 1 (cont')

...dumpblock

```
		(void) putc('\n', fx);
		for (i = 0; i < 2; i++) {
			if (*out[i] && (*out[i] != ' ' || *(po[i]) != ' ')) {
				if (i == 0)
					nums(i);
				if (i == 0 && *out[1])
					stars();
				putline(i);
				if (i == 0 && *out[1])
					fprintf(fx, star);
				if (i == 1)
					nums(i);
			}
		}
}

/*
 * put out a number line: dumpblock()
 */
static
nums(ix)
	int	ix;	/* index in out[] holding seq line */
{
	char		nline[P_LINE];
	register	i, j;
	register char	*pn, *px, *py;

	for (pn = nline, i = 0; i < lmax+P_SPC; i++, pn++)
		*pn = ' ';
	for (i = nc[ix], py = out[ix]; *py; py++, pn++) {
		if (*py == ' ' || *py == '-')
			*pn = ' ';
		else {
			if (i%10 == 0 || (i == 1 && nc[ix] != 1)) {
				j = (i < 0)? -i : i;
				for (px = pn; j; j /= 10, px--)
					*px = j%10 + '0';
				if (i < 0)
					*px = '-';
			}
			else
				*pn = ' ';
			i++;
		}
	}
	*pn = '\0';
	nc[ix] = i;
	for (pn = nline; *pn; pn++)
		(void) putc(*pn, fx);
	(void) putc('\n', fx);
}

/*
 * put out a line (name, [num], seq, [num]): dumpblock()
 */
static
putline(ix)
	int	ix;	{
```

nums

putline

Table 1 (cont')

...putline

```
	int		i;
	register char	*px;

	for (px = namex[ix], i = 0; *px && *px != ':'; px++, i++)
		(void) putc(*px, fx);
	for (; i < lmax+P_SPC; i++)
		(void) putc(' ', fx);

	/* these count from 1:
	 * ni[] is current element (from 1)
	 * nc[] is number at start of current line
	 */
	for (px = out[ix]; *px; px++)
		(void) putc(*px&0x7F, fx);
	(void) putc('\n', fx);
}

/*
 * put a line of stars (seqs always in out[0], out[1]): dumpblock()
 */
static
stars()
{
	int		i;
	register char	*p0, *p1, cx, *px;

	if (!*out[0] || (*out[0] == ' ' && *(po[0]) == ' ') ||
	   !*out[1] || (*out[1] == ' ' && *(po[1]) == ' '))
		return;
	px = star;
	for (i = lmax+P_SPC; i; i--)
		*px++ = ' ';

	for (p0 = out[0], p1 = out[1]; *p0 && *p1; p0++, p1++) {
		if (isalpha(*p0) && isalpha(*p1)) {

			if (xbm[*p0-'A']&xbm[*p1-'A']) {
				cx = '*';
				nm++;
			}
			else if (!dna && _day[*p0-'A'][*p1-'A'] > 0)
				cx = '.';
			else
				cx = ' ';
		}
		else
			cx = ' ';
		*px++ = cx;
	}
	*px++ = '\n';
	*px = '\0';
}
```

stars

Table 1 (cont')

```
/*
 * strip path or prefix from pn, return len: pr_align()
 */
static
stripname(pn)                                                    stripname
        char    *pn;        /* file name (may be path) */
{
        register char   *px, *py;

        py = 0;
        for (px = pn; *px; px++)
                if (*px == '/')
                        py = px + 1;
        if (py)
                (void) strcpy(pn, py);
        return(strlen(pn));

}
```


Table 1 (cont')

```
/*
 * cleanup() -- cleanup any tmp file
 * getseq() -- read in seq, set dna, len, maxlen
 * g_calloc() -- calloc() with error checkin
 * readjmps() -- get the good jmps, from tmp file if necessary
 * writejmps() -- write a filled array of jmps to a tmp file: nw()
 */
#include "nw.h"
#include <sys/file.h>

char    *jname = "/tmp/homgXXXXXX";          /* tmp file for jmps */
FILE    *fj;

int     cleanup();                           /* cleanup tmp file */
long    lseek();

/*
 * remove any tmp file if we blow
 */
cleanup(i)                                                          cleanup
        int     i;
{
        if (fj)
                (void) unlink(jname);
        exit(i);
}

/*
 * read, return ptr to seq, set dna, len, maxlen
 * skip lines starting with ';', '<', or '>'
 * seq in upper or lower case
 */
char    *
getseq(file, len)                                                   getseq
        char    *file;  /* file name */
        int     *len;   /* seq len */
{
        char            line[1024], *pseq;
        register char   *px, *py;
        int             natgc, tlen;
        FILE            *fp;

        if ((fp = fopen(file,"r")) == 0) {
                fprintf(stderr,"%s: can't read %s\n", prog, file);
                exit(1);
        }
        tlen = natgc = 0;
        while (fgets(line, 1024, fp)) {
                if (*line == ';' || *line == '<' || *line == '>')
                        continue;
                for (px = line; *px != '\n'; px++)
                        if (isupper(*px) || islower(*px))
                                tlen++;
        }
        if ((pseq = malloc((unsigned)(tlen+6))) == 0) {
                fprintf(stderr,"%s: malloc() failed to get %d bytes for %s\n", prog, tlen+6, file);
                exit(1);
        }
        pseq[0] = pseq[1] = pseq[2] = pseq[3] = '\0';
```

Table 1 (cont')

...getseq

```
        py = pseq + 4;
        *len = tlen;
        rewind(fp);

        while (fgets(line, 1024, fp)) {
                if (*line == ';' || *line == '<' || *line == '>')
                        continue;
                for (px = line; *px != '\n'; px++) {
                        if (isupper(*px))
                                *py++ = *px;
                        else if (islower(*px))
                                *py++ = toupper(*px);
                        if (index("ATGCU",*(py-1)))
                                natgc++;
                }
        }
        *py++ = '\0';
        *py = '\0';
        (void) fclose(fp);
        dna = natgc > (tlen/3);
        return(pseq+4);
}
```

g_calloc

```
char    *
g_calloc(msg, nx, sz)
        char    *msg;           /* program, calling routine */
        int     nx, sz;         /* number and size of elements */
{
        char            *px, *calloc();

        if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
                if (*msg) {
                        fprintf(stderr, "%s: g_calloc() failed %s (n=%d, sz=%d)\n", prog, msg, nx, sz);
                        exit(1);
                }
        }
        return(px);
}
```

readjmps

```
/*
 * get final jmps from dx[] or tmp file, set pp[], reset dmax: main()
 */
readjmps()
{
        int             fd = -1;
        int             siz, i0, i1;
        register  i, j, xx;

        if (fj) {
                (void) fclose(fj);
                if ((fd = open(jname, O_RDONLY, 0)) < 0) {
                        fprintf(stderr, "%s: can't open() %s\n", prog, jname);
                        cleanup(1);
                }
        }
        for (i = i0 = i1 = 0, dmax0 = dmax, xx = len0; ; i++) {
                while (1) {
                        for (j = dx[dmax].ijmp; j >= 0 && dx[dmax].jp.x[j] >= xx; j--)
                                ;
```


Table 1 (cont')

...readjmps

```
                    if (j < 0 && dx[dmax].offset && fj) {
                            (void) lseek(fd, dx[dmax].offset, 0);
                            (void) read(fd, (char *)&dx[dmax].jp, sizeof(struct jmp));
                            (void) read(fd, (char *)&dx[dmax].offset, sizeof(dx[dmax].offset));
                            dx[dmax].ijmp = MAXJMP-1;
                    }
                    else
                            break;
            }
            if (i >= JMPS) {
                    fprintf(stderr, "%s: too many gaps in alignment\n", prog);
                    cleanup(1);
            }
            if (j >= 0) {
                    siz = dx[dmax].jp.n[j];
                    xx = dx[dmax].jp.x[j];
                    dmax += siz;
                    if (siz < 0) {                  /* gap in second seq */
                            pp[1].n[i1] = -siz;
                            xx += siz;
                            /* id = xx - yy + len1 - 1
                             */
                            pp[1].x[i1] = xx - dmax + len1 - 1;
                            gapy++;
                            ngapy -= siz;
/* ignore MAXGAP when doing endgaps */
                            siz = (-siz < MAXGAP || endgaps)? -siz : MAXGAP;
                            i1++;
                    }
                    else if (siz > 0) { /* gap in first seq */
                            pp[0].n[i0] = siz;
                            pp[0].x[i0] = xx;
                            gapx++;
                            ngapx += siz;
/* ignore MAXGAP when doing endgaps */
                            siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
                            i0++;
                    }
            }
            else
                    break;
    }

    /* reverse the order of jmps
     */
    for (j = 0, i0--; j < i0; j++, i0--) {
            i = pp[0].n[j]; pp[0].n[j] = pp[0].n[i0]; pp[0].n[i0] = i;
            i = pp[0].x[j]; pp[0].x[j] = pp[0].x[i0]; pp[0].x[i0] = i;
    }
    for (j = 0, i1--; j < i1; j++, i1--) {
            i = pp[1].n[j]; pp[1].n[j] = pp[1].n[i1]; pp[1].n[i1] = i;
            i = pp[1].x[j]; pp[1].x[j] = pp[1].x[i1]; pp[1].x[i1] = i;
    }
    if (fd >= 0)
            (void) close(fd);
    if (fj) {
            (void) unlink(jname);
            fj = 0;
            offset = 0;
    }                                   }
```

Table 1 (cont')

writejmps

```
/*
 * write a filled jmp struct offset of the prev one (if any): nw()
 */
writejmps(ix)
        int     ix;
{
        char    *mktemp();

        if (!fj) {
                if (mktemp(jname) < 0) {
                        fprintf(stderr, "%s: can't mktemp() %s\n", prog, jname);
                        cleanup(1);
                }
                if ((fj = fopen(jname, "w")) == 0) {
                        fprintf(stderr, "%s: can't write %s\n", prog, jname);
                        exit(1);
                }
        }
        (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
        (void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
}
```


Table 2

PRO	XXXXXXXXXXXXXXX	(Length = 15 amino acids)
Comparison Protein	XXXXXYYYYYYY	(Length = 12 amino acids)

% amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =

5 divided by 15 = 33.3%

Table 3

PRO	XXXXXXXXXX	(Length = 10 amino acids)
Comparison Protein	XXXXXYYYYYYZZYZ	(Length = 15 amino acids)

% amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =

5 divided by 10 = 50%

Table 4

PRO-DNA	NNNNNNNNNNNNNN	(Length = 14 nucleotides)
Comparison DNA	NNNNNNLLLLLLLLLL	(Length = 16 nucleotides)

% nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

6 divided by 14 = 42.9%

Table 5

PRO-DNA	NNNNNNNNNNNN	(Length = 12 nucleotides)
Comparison DNA	NNNNLLLVV	(Length = 9 nucleotides)

% nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

4 divided by 12 = 33.3%

II. Compositions and Methods of the Invention

A. Full-length SRT Polypeptides

The present invention provides newly identified and isolated polynucleotide sequences encoding at least a portion of full-length human polypeptides referred to in the present application as SRT polypeptides. In particular, cDNAs encoding at least a portion of SRT polypeptides have been identified and isolated, as disclosed in further detail in the Examples below. For sake of simplicity, in the present specification the polypeptides encoded by nucleic acid molecules disclosed herein as well as all further native homologues and variants included in the foregoing definition of SRT, will be referred to as "SRT", regardless of their origin or mode of preparation.

B. SRT Polypeptide Variants

In addition to the native sequence SRT polypeptides described herein, it is contemplated that SRT variants can be prepared. SRT variants can be prepared by introducing appropriate nucleotide changes into the SRT DNA, and/or by synthesis of the desired SRT polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of the SRT, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

Variations in the native sequence SRT or in various domains of the SRT described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a substitution, deletion or insertion of one or more codons encoding the SRT that results in a change in the amino acid sequence of the SRT as compared with the native sequence SRT. Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the SRT. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the SRT with that of homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i.e., conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 1 to 5 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

SRT polypeptide fragments are provided herein. Such fragments may be truncated at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full-length native protein. Certain fragments lack amino acid residues that are not essential for a desired biological activity of the SRT polypeptide.

SRT fragments may be prepared by any of a number of conventional techniques. Desired peptide fragments may be chemically synthesized. An alternative approach involves generating SRT fragments by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable restriction enzymes and isolating the

desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired polypeptide fragment, by polymerase chain reaction (PCR). Oligonucleotides that define the desired termini of the DNA fragment are employed at the 5' and 3' primers in the PCR. Preferably, SRT polypeptide fragments share at least one biological and/or immunological activity with the corresponding native SRT polypeptide.

In particular embodiments, conservative substitutions of interest are shown in Table 6 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial changes, denominated exemplary substitutions in Table 6, or as further described below in reference to amino acid classes, are introduced and the products screened.

Table 6

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	val; leu; ile	val
Arg (R)	lys; gln; asn	lys
Asn (N)	gln; his; lys; arg	gln
Asp (D)	glu	glu
Cys (C)	ser	ser
Gln (Q)	asn	asn
Glu (E)	asp	asp
Gly (G)	pro; ala	ala
His (H)	asn; gln; lys; arg	arg
Ile (I)	leu; val; met; ala; phe; norleucine	leu
Leu (L)	norleucine; ile; val; met; ala; phe	ile
Lys (K)	arg; gln; asn	arg
Met (M)	leu; phe; ile	leu
Phe (F)	leu; val; ile; ala; tyr	leu
Pro (P)	ala	ala
Ser (S)	thr	thr
Thr (T)	ser	ser
Trp (W)	tyr; phe	tyr
Tyr (Y)	trp; phe; thr; ser	phe
Val (V)	ile; leu; met; phe; ala; norleucine	leu

Substantial modifications in function or immunological identity of the SRT polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

(1) hydrophobic: norleucine, met, ala, val, leu, ile;

(2) neutral hydrophilic: cys, ser, thr;

(3) acidic: asp, glu;

(4) basic: asn, gln, his, lys, arg;

(5) residues that influence chain orientation: gly, pro; and

(6) aromatic: trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter et al., Nucl. Acids Res., 13:4331 (1986); Zoller et al., Nucl. Acids Res., 10:6487 (1987)], cassette mutagenesis [Wells et al., Gene, 34:315 (1985)], restriction selection mutagenesis [Wells et al., Philos. Trans. R. Soc. London SerA, 317:415 (1986)] or other known techniques can be performed on the cloned DNA to produce the SRT variant DNA.

Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, Science, 244: 1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, The Proteins, (W.H. Freeman & Co., N.Y.); Chothia, J. Mol. Biol., 150:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

C. Modifications of SRT Polypeptides

Covalent modifications of SRT polypeptides are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of a SRT polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C- terminal residues of the SRT. Derivatization with bifunctional agents is useful, for instance, for crosslinking SRT to a water-insoluble support matrix or surface for use in the method for purifying anti-SRT antibodies, and vice-versa. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimidate.

Other modifications include deamidation of glutaminyl and asparaginyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α-amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the SRT polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence

SRT (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence SRT. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Addition of glycosylation sites to the SRT polypeptide may be accomplished by altering the amino acid sequence. The alteration may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues to the native sequence SRT (for O-linked glycosylation sites). The SRT amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the SRT polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate moieties on the SRT polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e.g., in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, CRC Crit. Rev. Biochem., pp. 259-306 (1981).

Removal of carbohydrate moieties present on the SRT polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin et al., Arch. Biochem. Biophys., 259:52 (1987) and by Edge et al., Anal. Biochem. 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., Meth. Enzymol., 138:350 (1987).

Another type of covalent modification of SRT comprises linking the SRT polypeptide to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

The SRT polypeptides of the present invention may also be modified in a way to form chimeric molecules comprising SRT fused to another, heterologous polypeptide or amino acid sequence.

In one embodiment, such a chimeric molecule comprises a fusion of the SRT with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the SRT. The presence of such epitope-tagged forms of the SRT can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the SRT to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-his) or poly-histidine-glycine (poly-his-gly) tags; the flu HA tag polypeptide and its antibody 12CA5 [Field et al., Mol. Cell. Biol., 8:2159-2165 (1988)]; the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan et al., Molecular and Cellular Biology, 5:3610-3616 (1985)]; and the Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky et al., Protein Engineering, 3(6):547-553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp et al., BioTechnology, 6:1204-1210 (1988)]; the KT3 epitope peptide [Martin et al., Science, 255:192-194 (1992)]; an α-tubulin epitope peptide [Skinner et al., J. Biol. Chem., 266:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-

Freyermuth et al., Proc. Natl. Acad. Sci. USA, 87:6393-6397 (1990)].

In an alternative embodiment, the chimeric molecule may comprise a fusion of the SRT with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule (also referred to as an "immunoadhesin"), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of a SRT polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred embodiment, the immunoglobulin fusion includes the hinge, CH2 and CH3, or the hinge, CH1, CH2 and CH3 regions of an IgG1 molecule. For the production of immunoglobulin fusions see also US Patent No. 5,428,130 issued June 27, 1995.

D. Preparation of SRT Polypeptides

The description below relates primarily to production of SRT by culturing cells transformed or transfected with a vector containing SRT nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare SRT. For instance, the SRT sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart et al., Solid-Phase Peptide Synthesis, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, J. Am. Chem. Soc., 85:2149-2154 (1963)]. *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the SRT may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the full-length SRT.

1. Isolation of DNA Encoding SRT

DNA encoding SRT may be obtained from a cDNA library prepared from tissue believed to possess the SRT mRNA and to express it at a detectable level. Accordingly, human SRT DNA can be conveniently obtained from a cDNA library prepared from human tissue, such as described in the Examples. The SRT-encoding gene may also be obtained from a genomic library or by known synthetic procedures (e.g., automated nucleic acid synthesis).

Libraries can be screened with probes (such as antibodies to the SRT or oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it, wherein those probes may be based upon the polynucleotide sequences shown in the accompanying figures. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook et al., Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1989). An alternative means to isolate the gene encoding SRT is to use PCR methodology [Sambrook et al., supra; Dieffenbach et al., PCR Primer: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1995)].

The Examples below describe techniques for screening a cDNA library. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like ^{32}P-labeled

ATP, biotinylation or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook et al., supra.

Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined using methods known in the art and as described herein.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook et al., supra, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

2. Selection and Transformation of Host Cells

Host cells are transfected or transformed with expression or cloning vectors described herein for SRT production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: a Practical Approach, M. Butler, ed. (IRL Press, 1991) and Sambrook et al., supra.

Methods of eukaryotic cell transfection and prokaryotic cell transformation are known to the ordinarily skilled artisan, for example, $CaCl_2$, $CaPO_4$, liposome-mediated and electroporation. Depending on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook et al., supra, or electroporation is generally used for prokaryotes. Infection with *Agrobacterium tumefaciens* is used for transformation of certain plant cells, as described by Shaw et al., Gene, 23:315 (1983) and WO 89/05859 published 29 June 1989. For mammalian cells without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, Virology, 52:456-457 (1978) can be employed. General aspects of mammalian cell host system transfections have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van Solingen et al., J. Bact., 130:946 (1977) and Hsiao et al., Proc. Natl. Acad. Sci. (USA), 76:3829 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, e.g., polybrene, polyornithine, may also be used. For various techniques for transforming mammalian cells, see Keown et al., Methods in Enzymology, 185:527-537 (1990) and Mansour et al., Nature, 336:348-352 (1988).

Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325) and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include

Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41P disclosed in DD 266,710 published 12 April 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype *tonA* ; *E. coli* W3110 strain 9E4, which has the complete genotype *tonA ptr3*; *E. coli* W3110 strain 27C7 (ATCC 55,244), which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT kan^r*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7 ilvG kan^r*; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, e.g., PCR or other nucleic acid polymerase reactions, are suitable.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for SRT-encoding vectors. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* (Beach and Nurse, Nature, 290: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 4,943,529; Fleer et al., Bio/Technology, 9:968-975 (1991)) such as, e.g., *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt et al., J. Bacteriol., 737 [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickeramii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilarum* (ATCC 36,906; Van den Berg et al., Bio/Technology, 8:135 (1990)), *K. thermotolerans*, and *K. marxianus; yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreekrishna et al., J. Basic Microbiol., 28:265-278 [1988]); *Candida; Trichoderma reesia* (EP 244,234); *Neurospora crassa* (Case et al., Proc. Natl. Acad. Sci. USA, 76:5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, e.g., *Neurospora, Penicillium, Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance et al., Biochem. Biophys. Res. Commun., 112:284-289 [1983]; Tilburn et al., Gene, 26:205-221 [1983]; Yelton et al., Proc. Natl. Acad. Sci. USA, 81: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, EMBO J., 4:475-479 [1985]). Methylotropic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula, Candida, Kloeckera, Pichia, Saccharomyces, Torulopsis,* and *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, The Biochemistry of Methylotrophs, 269 (1982).

Suitable host cells for the expression of glycosylated SRT are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as Drosophila S2 and Spodoptera Sf9, as well as plant cells. Examples of useful mammalian host cell lines include Chinese hamster ovary (CHO) and COS cells. More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., J.

Gen Virol., 36:59 (1977)); Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, Proc. Natl. Acad. Sci. USA, 77:4216 (1980)); mouse sertoli cells (TM4, Mather, Biol. Reprod., 23:243-251 (1980)); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor (MMT 060562, ATCC CCL51). The selection of the appropriate host cell is deemed to be within the skill in the art.

3. Selection and Use of a Replicable Vector

The nucleic acid (e.g., cDNA or genomic DNA) encoding SRT may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally include, but are not limited to, one or more of a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques which are known to the skilled artisan.

The SRT may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the SRT-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e.g., the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces* α-factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2μ plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for *Bacilli*.

An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the SRT-encoding nucleic acid, such as DHFR or thymidine kinase. An appropriate

host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described by Urlaub et al., Proc. Natl. Acad. Sci. USA, 77:4216 (1980). A suitable selection gene for use in yeast is the *trp*1 gene present in the yeast plasmid YRp7 [Stinchcomb et al., Nature, 282:39 (1979); Kingsman et al., Gene, 7:141 (1979); Tschemper et al., Gene, 10:157 (1980)]. The *trp*1 gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1 [Jones, Genetics, 85:12 (1977)].

Expression and cloning vectors usually contain a promoter operably linked to the SRT-encoding nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the β-lactamase and lactose promoter systems [Chang et al., Nature, 275:615 (1978); Goeddel et al., Nature, 281:544 (1979)], alkaline phosphatase, a tryptophan (trp) promoter system [Goeddel, Nucleic Acids Res., 8:4057 (1980); EP 36,776], and hybrid promoters such as the tac promoter [deBoer et al., Proc. Natl. Acad. Sci. USA, 80:21-25 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding SRT.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman et al., J. Biol. Chem., 255:2073 (1980)] or other glycolytic enzymes [Hess et al., J. Adv. Enzyme Reg., 7:149 (1968); Holland, Biochemistry, 17:4900 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657.

SRT transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

Transcription of a DNA encoding the SRT by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, α-fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or

3' to the SRT coding sequence, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding SRT.

Still other methods, vectors, and host cells suitable for adaptation to the synthesis of SRT in recombinant vertebrate cell culture are described in Gething et al., Nature, 293:620-625 (1981); Mantei et al., Nature, 281:40-46 (1979); EP 117,060; and EP 117,058.

4. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, Proc. Natl. Acad. Sci. USA, 77:5201-5205 (1980)], dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence SRT polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to SRT DNA and encoding a specific antibody epitope.

5. Purification of Polypeptide

Forms of SRT may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g. Triton-X 100) or by enzymatic cleavage. Cells employed in expression of SRT can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

It may be desired to purify SRT from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the SRT. Various methods of protein purification may be employed and such

methods are known in the art and described for example in Deutscher, Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular SRT produced.

E. Uses for SRT Polynucleotides and Polypeptides

SRT nucleotide sequences (and/or their complements) disclosed herein have various applications in the art of molecular biology, including for example uses as hybridization probes, in chromosome and gene mapping, in tissue typing, disease tissue detection, in PCR technologies, in screening for new therapeutic molecules and in the generation of anti-sense RNA and DNA. SRT nucleic acid will also be useful for the preparation of SRT polypeptides by the recombinant techniques described herein.

The SRT polynucleotides disclosed herein, or portions thereof, may be used as hybridization probes for a cDNA library to isolate the full-length SRT cDNA or to isolate still other cDNAs (for instance, those encoding naturally-occurring variants of SRT or SRT from other species) which have a desired sequence identity to the SRT sequence of interest. Optionally, the length of the probes will be about 20 to about 50 bases. The hybridization probes may be derived from at least partially novel regions of the nucleotide sequences disclosed herein wherein those regions may be determined without undue experimentation or from genomic sequences including promoters, enhancer elements and introns of native sequence SRT. By way of example, a screening method will comprise isolating the coding region of the SRT gene using the known DNA sequence to synthesize a selected probe of about 40 bases. Hybridization probes may be labeled by a variety of labels, including radionucleotides such as ^{32}P or ^{35}S, or enzymatic labels such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems. Labeled probes having a sequence complementary to that of the SRT gene of the present invention can be used to screen libraries of human cDNA, genomic DNA or mRNA to determine which members of such libraries the probe hybridizes to. Hybridization techniques are described in further detail in the Examples below.

PCR as described in U.S. Pat. Nos. 4,683,195; 4,800,195; and 4,965,188 provides additional uses for oligonucleotides based upon the polynucleotide sequences disclosed in the accompanying figures. Such oligomers are generally chemically synthesized, but they may be of recombinant origin or a mixture of both. Oligomers generally comprise two nucleotide sequences, one with sense orientation (5' to 3') and one with antisense (3' to 5') employed under optimized conditions for identification of a specific gene or diagnostic use. The same two oligomers, nested sets of oligomers, or even a degenerate pool of oligomers may be employed under less stringent conditions for identification and/or quantitation of closely related DNA or RNA sequences.

Full length genes may be cloned utilizing partial nucleotide sequence and various methods known in the art. Gobinda et al. PCR Methods Applic. 2:318-322 (1993) disclose "restriction-site PCR" as a direct method which uses universal primers to retrieve unknown sequence adjacent to a known locus. First, genomic DNA is amplified in the presence of primer to linker and a primer specific to the known region. The amplified sequences are subjected to a second round of PCR with the same linker primer and another specific primer internal to the first one. Products of each round of PCR are transcribed with an appropriate RNA polymerase and sequenced

using reverse transcriptase. Gobinda et al present data concerning Factor IX for which they identified a conserved stretch of 20 nucleotides in the 3' noncoding region of the gene.

Inverse PCR is the first method to report successful acquisition of unknown sequences starting with primers based on a known region (Triglia et al., Nucleic Acids Res. 16:8186 (1988). The method uses several restriction enzymes to generate a suitable fragment in the known region of a gene. The fragment is then circularized by intramolecular ligation and used as a PCR template. Divergent primers are designed from the known region. The multiple rounds of restriction enzyme digestions and ligations that are necessary prior to PCR make the procedure slow and expensive (Gobinda et al, *supra*).

Capture PCR (Lagerstrom et al., PCR Methods Applic. 1:111-119 (1991) is a method for PCR amplification of DNA fragments adjacent to a known sequence in human and YAC DNA. As noted by Gobinda et al. (*supra*), capture PCR also requires multiple restriction enzyme digestions and ligations to place an engineered double-stranded sequence into an unknown portion of the DNA molecule before PCR. Although the restriction and ligation reactions are carried out simultaneously, the requirements for extension, immobilization and two rounds of PCR and purification prior to sequencing render the method cumbersome and time consuming.

Parker et al., Nucleic Acids Res. 19:3055-3060 (1991) teach walking PCR, a method for targeted gene walking which permits retrieval of unknown sequence. PromoterFinder™ is a new kit available from Clontech (Palo Alto, Calif.) which uses PCR and primers derived from p53 to walk in genomic DNA. Nested primers and special PromoterFinder libraries are used to detect upstream sequences such as promoters and regulatory elements. This process avoids the need to screen libraries and is useful in finding intron/exon junctions.

Another new PCR method, "Improved Method for Obtaining Full Length cDNA Sequences" (see U.S. Patent No. 5,817,479, issued October 6, 1998), employs XL-PCR (Perkin-Elmer, Foster City, Calif.) to amplify and extend partial nucleotide sequence into longer pieces of DNA. This method was developed to allow a single researcher to process multiple genes (up to 20 or more) at one time and to obtain an extended (possibly full-length) sequence within 6-10 days. This new method replaces methods which use labelled probes to screen plasmid libraries and allow one researcher to process only about 3-5 genes in 14-40 days.

In the first step, which can be performed in about two days, any two of a plurality of primers are designed and synthesized based on a known partial sequence. In step 2, which takes about six to eight hours, the sequence is extended by PCR amplification of a selected library. Steps 3 and 4, which take about one day, are purification of the amplified cDNA and its ligation into an appropriate vector. Step 5, which takes about one day, involves transforming and growing up host bacteria. In step 6, which takes approximately five hours, PCR is used to screen bacterial clones for extended sequence. The final steps, which take about one day, involve the preparation and sequencing of selected clones.

If the full length cDNA has not been obtained, the entire procedure is repeated using either the original library or some other preferred library. The preferred library may be one that has been size-selected to include only larger cDNAs or may consist of single or combined commercially available libraries, eg. lung, liver, heart and brain from Gibco/BRL (Gaithersburg, Md.). The cDNA library may have been prepared with oligo (dT) or random priming. Random primed libraries are preferred in that they will contain more sequences which contain 5' ends of genes. A randomly primed library may be particularly useful if an oligo (dT) library does not

yield a complete gene.

The nucleotide sequence for any particular polynucleotide shown in the accompanying figures can also be used to generate probes for mapping the native genomic sequence. The sequence may be mapped to a particular chromosome or to a specific region of the chromosome using well known techniques. These include *in situ* hybridization to chromosomal spreads (Verma et al., "Human Chromosomes: A Manual of Basic Techniques", Pergamon Press, New York City, 1988), flow-sorted chromosomal preparations, or artificial chromosome constructions such as yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions or single chromosome cDNA libraries.

In situ hybridization of chromosomal preparations and physical mapping techniques such as linkage analysis using established chromosomal markers are invaluable in extending genetic maps. Examples of genetic maps can be found in the 1994 Genome Issue of Science (265:1981f). Often the placement of a gene on the chromosome of another mammalian species may reveal associated markers even if the number or arm of a particular human chromosome is not known. New partial nucleotide sequences can be assigned to chromosomal arms, or parts thereof, by physical mapping. This provides valuable information to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once a disease or syndrome, such as ataxia telangiectasia (AT), has been crudely localized by genetic linkage to a particular genomic region, for example, AT to 11q22-23 (Gatti et al., Nature 336:577-580 (1988), any sequences mapping to that area may represent genes for further investigation. The nucleotide sequences of the subject invention may also be used to detect differences in the chromosomal location of nucleotide sequences due to translocation, inversion, etc., between normal and carrier or affected individuals.

The partial nucleotide sequence encoding a particular SRT polypeptide may be used to produce an amino acid sequence using well known methods of recombinant DNA technology. The amino acid or peptide may be expressed in a variety of host cells, either prokaryotic or eukaryotic. Host cells may be from the same species from which the nucleotide sequence was derived or from a different species. Advantages of producing an amino acid sequence or peptide by recombinant DNA technology include obtaining adequate amounts for purification and the availability of simplified purification procedures.

Cells transformed with an SRT nucleotide sequence may be cultured under conditions suitable for the expression and recovery of peptide from cell culture as described above. The peptide produced by a recombinant cell may be secreted or may be contained intracellularly depending on the sequence itself and/or the vector used. In general, it is more convenient to prepare recombinant proteins in secreted form, and this is accomplished by ligating SRT to a recombinant nucleotide sequence which directs its movement through a particular prokaryotic or eukaryotic cell membrane. Other recombinant constructions may join SRT to nucleotide sequence encoding a polypeptide domain which will facilitate protein purification (Kroll et al., DNA Cell Biol. 12:441-53 (1993).

Other useful fragments of the SRT nucleic acids include antisense or sense oligonucleotides comprising a singe-stranded nucleic acid sequence (either RNA or DNA) capable of binding to target SRT mRNA (sense) or SRT DNA (antisense) sequences. Antisense or sense oligonucleotides, according to the present invention, comprise a fragment of the coding region of SRT DNA. Such a fragment generally comprises at least about 14 nucleotides, preferably from about 14 to 30 nucleotides. The ability to derive an antisense or a sense

oligonucleotide, based upon a cDNA sequence encoding a given protein is described in, for example, Stein and Cohen (Cancer Res. 48:2659, 1988) and van der Krol et al. (BioTechniques 6:958, 1988).

Binding of antisense or sense oligonucleotides to target nucleic acid sequences results in the formation of duplexes that block transcription or translation of the target sequence by one of several means, including enhanced degradation of the duplexes, premature termination of transcription or translation, or by other means. The antisense oligonucleotides thus may be used to block expression of SRT proteins. Antisense or sense oligonucleotides further comprise oligonucleotides having modified sugar-phosphodiester backbones (or other sugar linkages, such as those described in WO 91/06629) and wherein such sugar linkages are resistant to endogenous nucleases. Such oligonucleotides with resistant sugar linkages are stable *in vivo* (i.e., capable of resisting enzymatic degradation) but retain sequence specificity to be able to bind to target nucleotide sequences.

Other examples of sense or antisense oligonucleotides include those oligonucleotides which are covalently linked to organic moieties, such as those described in WO 90/10048, and other moieties that increases affinity of the oligonucleotide for a target nucleic acid sequence, such as poly-(L-lysine). Further still, intercalating agents, such as ellipticine, and alkylating agents or metal complexes may be attached to sense or antisense oligonucleotides to modify binding specificities of the antisense or sense oligonucleotide for the target nucleotide sequence.

Antisense or sense oligonucleotides may be introduced into a cell containing the target nucleic acid sequence by any gene transfer method, including, for example, $CaPO_4$-mediated DNA transfection, electroporation, or by using gene transfer vectors such as Epstein-Barr virus. In a preferred procedure, an antisense or sense oligonucleotide is inserted into a suitable retroviral vector. A cell containing the target nucleic acid sequence is contacted with the recombinant retroviral vector, either *in vivo* or *ex vivo*. Suitable retroviral vectors include, but are not limited to, those derived from the murine retrovirus M-MuLV, N2 (a retrovirus derived from M-MuLV), or the double copy vectors designated DCT5A, DCT5B and DCT5C (see WO 90/13641).

Sense or antisense oligonucleotides also may be introduced into a cell containing the target nucleotide sequence by formation of a conjugate with a ligand binding molecule, as described in WO 91/04753. Suitable ligand binding molecules include, but are not limited to, cell surface receptors, growth factors, other cytokines, or other ligands that bind to cell surface receptors. Preferably, conjugation of the ligand binding molecule does not substantially interfere with the ability of the ligand binding molecule to bind to its corresponding molecule or receptor, or block entry of the sense or antisense oligonucleotide or its conjugated version into the cell.

Alternatively, a sense or an antisense oligonucleotide may be introduced into a cell containing the target nucleic acid sequence by formation of an oligonucleotide-lipid complex, as described in WO 90/10448. The sense or antisense oligonucleotide-lipid complex is preferably dissociated within the cell by an endogenous lipase.

The probes may also be employed in PCR techniques to generate a pool of sequences for identification of closely related SRT coding sequences.

Nucleotide sequences encoding an SRT can also be used to construct hybridization probes for mapping the gene which encodes that SRT and for the genetic analysis of individuals with genetic disorders. The nucleotide sequences provided herein may be mapped to a chromosome and specific regions of a chromosome

using known techniques, such as *in situ* hybridization, linkage analysis against known chromosomal markers, and hybridization screening with libraries.

When the coding sequences for SRT encode a protein which binds to another protein (example, where the SRT is a receptor), the SRT can be used in assays to identify the other proteins or molecules involved in the binding interaction. By such methods, inhibitors of the receptor/ligand binding interaction can be identified. Proteins involved in such binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction. Also, the receptor SRT can be used to isolate correlative ligand(s). Screening assays can be designed to find lead compounds that mimic the biological activity of a native SRT or a receptor for SRT. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates. Small molecules contemplated include synthetic organic or inorganic compounds. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well characterized in the art.

Nucleic acids which encode SRT or its modified forms can also be used to generate either transgenic animals or "knock out" animals which, in turn, are useful in the development and screening of therapeutically useful reagents. A transgenic animal (e.g., a mouse or rat) is an animal having cells that contain a transgene, which transgene was introduced into the animal or an ancestor of the animal at a prenatal, e.g., an embryonic stage. A transgene is a DNA which is integrated into the genome of a cell from which a transgenic animal develops. In one embodiment, cDNA encoding SRT can be used to clone genomic DNA encoding SRT in accordance with established techniques and the genomic sequences used to generate transgenic animals that contain cells which express DNA encoding SRT. Methods for generating transgenic animals, particularly animals such as mice or rats, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009. Typically, particular cells would be targeted for SRT transgene incorporation with tissue-specific enhancers. Transgenic animals that include a copy of a transgene encoding SRT introduced into the germ line of the animal at an embryonic stage can be used to examine the effect of increased expression of DNA encoding SRT. Such animals can be used as tester animals for reagents thought to confer protection from, for example, pathological conditions associated with its overexpression. In accordance with this facet of the invention, an animal is treated with the reagent and a reduced incidence of the pathological condition, compared to untreated animals bearing the transgene, would indicate a potential therapeutic intervention for the pathological condition.

Alternatively, non-human homologues of SRT can be used to construct a SRT "knock out" animal which has a defective or altered gene encoding SRT as a result of homologous recombination between the endogenous gene encoding SRT and altered genomic DNA encoding SRT introduced into an embryonic stem cell of the animal. For example, cDNA encoding SRT can be used to clone genomic DNA encoding SRT in accordance with established techniques. A portion of the genomic DNA encoding SRT can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see e.g., Thomas and Capecchi, Cell, 51:503 (1987) for a description of homologous recombination vectors]. The vector

is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see e.g., Li et al., Cell, 69:915 (1992)]. The selected cells are then injected into a blastocyst of an animal (e.g., a mouse or rat) to form aggregation chimeras [see e.g., Bradley, in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E. J. Robertson, ed. (IRL, Oxford, 1987), pp. 113-152]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of the SRT polypeptide.

Nucleic acid encoding the SRT polypeptides may also be used in gene therapy. In gene therapy applications, genes are introduced into cells in order to achieve *in vivo* synthesis of a therapeutically effective genetic product, for example for replacement of a defective gene. "Gene therapy" includes both conventional gene therapy where a lasting effect is achieved by a single treatment, and the administration of gene therapeutic agents, which involves the one time or repeated administration of a therapeutically effective DNA or mRNA. Antisense RNAs and DNAs can be used as therapeutic agents for blocking the expression of certain genes *in vivo*. It has already been shown that short antisense oligonucleotides can be imported into cells where they act as inhibitors, despite their low intracellular concentrations caused by their restricted uptake by the cell membrane. (Zamecnik et al., Proc. Natl. Acad. Sci. USA 83:4143-4146 [1986]). The oligonucleotides can be modified to enhance their uptake, e.g. by substituting their negatively charged phosphodiester groups by uncharged groups.

There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. The currently preferred *in vivo* gene transfer techniques include transfection with viral (typically retroviral) vectors and viral coat protein-liposome mediated transfection (Dzau et al., Trends in Biotechnology 11, 205-210 [1993]). In some situations it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins which bind to a cell surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, e.g. capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu et al., J. Biol. Chem. 262, 4429-4432 (1987); and Wagner et al., Proc. Natl. Acad. Sci. USA 87, 3410-3414 (1990). For review of gene marking and gene therapy protocols see Anderson et al., Science 256, 808-813 (1992).

The SRT polypeptides described herein may also be employed as molecular weight markers for protein electrophoresis purposes.

The nucleic acid molecules encoding the SRT polypeptides or fragments thereof described herein are useful for chromosome identification. In this regard, there exists an ongoing need to identify new chromosome markers, since relatively few chromosome marking reagents, based upon actual sequence data are presently available. Each SRT nucleic acid molecule of the present invention can be used as a chromosome marker.

The SRT polypeptides and nucleic acid molecules of the present invention may also be used for tissue typing, wherein the SRT polypeptides of the present invention may be differentially expressed in one tissue as compared to another, for example in a diseased tissue versus a normal tissue. SRT nucleic acid molecules will find use for generating probes for PCR, Northern analysis, Southern analysis and Western analysis.

The SRT polypeptides described herein and antibodies thereagainst may also be employed as therapeutic agents. The SRT polypeptides of the present invention can be formulated according to known methods to prepare pharmaceutically useful compositions, whereby the SRT product hereof is combined in admixture with a pharmaceutically acceptable carrier vehicle. Therapeutic formulations are prepared for storage by mixing the active ingredient having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone, amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, PLURONICS™ or PEG.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes, prior to or following lyophilization and reconstitution.

Therapeutic compositions herein generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

The route of administration is in accord with known methods, e.g. injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial or intralesional routes, topical administration, or by sustained release systems.

Dosages and desired drug concentrations of pharmaceutical compositions of the present invention may vary depending on the particular use envisioned. The determination of the appropriate dosage or route of administration is well within the skill of an ordinary physician. Animal experiments provide reliable guidance for the determination of effective doses for human therapy. Interspecies scaling of effective doses can be performed following the principles laid down by Mordenti, J. and Chappell, W. "The use of interspecies scaling in toxicokinetics" In Toxicokinetics and New Drug Development, Yacobi et al., Eds., Pergamon Press, New York 1989, pp. 42-96.

When *in vivo* administration of a SRT polypeptide or agonist or antagonist thereof is employed, normal dosage amounts may vary from about 10 ng/kg to up to 100 mg/kg of mammal body weight or more per day,

preferably about 1 μg/kg/day to 10 mg/kg/day, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature; see, for example, U.S. Pat. Nos. 4,657,760; 5,206,344; or 5,225,212. It is anticipated that different formulations will be effective for different treatment compounds and different disorders, that administration targeting one organ or tissue, for example, may necessitate delivery in a manner different from that to another organ or tissue.

Where sustained-release administration of a SRT polypeptide is desired in a formulation with release characteristics suitable for the treatment of any disease or disorder requiring administration of the SRT polypeptide, microencapsulation of the SRT polypeptide is contemplated. Microencapsulation of recombinant proteins for sustained release has been successfully performed with human growth hormone (rhGH), interferon- (rhIFN-), interleukin-2, and MN rgp120. Johnson et al., Nat. Med., 2:795-799 (1996); Yasuda, Biomed. Ther., 27:1221-1223 (1993); Hora et al., Bio/Technology, 8:755-758 (1990); Cleland, "Design and Production of Single Immunization Vaccines Using Polylactide Polyglycolide Microsphere Systems," in Vaccine Design: The Subunit and Adjuvant Approach, Powell and Newman, eds, (Plenum Press: New York, 1995), pp. 439-462; WO 97/03692, WO 96/40072, WO 96/07399; and U.S. Pat. No. 5,654,010.

The sustained-release formulations of these proteins were developed using poly-lactic-coglycolic acid (PLGA) polymer due to its biocompatibility and wide range of biodegradable properties. The degradation products of PLGA, lactic and glycolic acids, can be cleared quickly within the human body. Moreover, the degradability of this polymer can be adjusted from months to years depending on its molecular weight and composition. Lewis, "Controlled release of bioactive agents from lactide/glycolide polymer," in: M. Chasin and R. Langer (Eds.), Biodegradable Polymers as Drug Delivery Systems (Marcel Dekker: New York, 1990), pp. 1-41.

This invention encompasses methods of screening compounds to identify those that mimic the SRT polypeptide (agonists) or prevent the effect of the SRT polypeptide (antagonists). Screening assays for antagonist drug candidates are designed to identify compounds that bind or complex with the SRT polypeptides encoded by the genes identified herein, or otherwise interfere with the interaction of the encoded polypeptides with other cellular proteins. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates.

The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays, and cell-based assays, which are well characterized in the art.

All assays for antagonists are common in that they call for contacting the drug candidate with a SRT polypeptide encoded by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the SRT polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, e.g., on a microtiter plate, by covalent or non-covalent attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the SRT polypeptide and drying. Alternatively, an immobilized antibody, e.g., a monoclonal antibody, specific for the SRT polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed

by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized component, e.g., the coated surface containing the anchored component. When the reaction is complete, the non-reacted components are removed, e.g., by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labeled antibody specifically binding the immobilized complex.

If the candidate compound interacts with but does not bind to a particular SRT polypeptide encoded by a gene identified herein, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, e.g., cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers (Fields and Song, Nature (London), 340:245-246 (1989); Chien et al., Proc. Natl. Acad. Sci. USA, 88:9578-9582 (1991)) as disclosed by Chevray and Nathans, Proc. Natl. Acad. Sci. USA, 89: 5789-5793 (1991). Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, the other one functioning as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a GAL1-*lacZ* reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for β-galactosidase. A complete kit (MATCHMAKER™) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

Compounds that interfere with the interaction of a gene encoding a SRT polypeptide identified herein and other intra- or extracellular components can be tested as follows: usually a reaction mixture is prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

To assay for antagonists, the SRT polypeptide may be added to a cell along with the compound to be screened for a particular activity and the ability of the compound to inhibit the activity of interest in the presence

of the SRT polypeptide indicates that the compound is an antagonist to the SRT polypeptide. Alternatively, antagonists may be detected by combining the SRT polypeptide and a potential antagonist with membrane-bound SRT polypeptide receptors or recombinant receptors under appropriate conditions for a competitive inhibition assay. The SRT polypeptide can be labeled, such as by radioactivity, such that the number of SRT polypeptide molecules bound to the receptor can be used to determine the effectiveness of the potential antagonist. The gene encoding the receptor can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting. Coligan et al., Current Protocols in Immun., 1(2): Chapter 5 (1991). Preferably, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the SRT polypeptide and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the SRT polypeptide. Transfected cells that are grown on glass slides are exposed to labeled SRT polypeptide. The SRT polypeptide can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase. Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an interactive sub-pooling and re-screening process, eventually yielding a single clone that encodes the putative receptor.

As an alternative approach for receptor identification, labeled SRT polypeptide can be photoaffinity-linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE and exposed to X-ray film. The labeled complex containing the receptor can be excised, resolved into peptide fragments, and subjected to protein micro-sequencing. The amino acid sequence obtained from micro- sequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the gene encoding the putative receptor.

In another assay for antagonists, mammalian cells or a membrane preparation expressing the receptor would be incubated with labeled SRT polypeptide in the presence of the candidate compound. The ability of the compound to enhance or block this interaction could then be measured.

More specific examples of potential antagonists include an oligonucleotide that binds to the fusions of immunoglobulin with SRT polypeptide, and, in particular, antibodies including, without limitation, poly- and monoclonal antibodies and antibody fragments, single-chain antibodies, anti-idiotypic antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. Alternatively, a potential antagonist may be a closely related protein, for example, a mutated form of the SRT polypeptide that recognizes the receptor but imparts no effect, thereby competitively inhibiting the action of the SRT polypeptide.

Another potential SRT polypeptide antagonist is an antisense RNA or DNA construct prepared using antisense technology, where, e.g., an antisense RNA or DNA molecule acts to block directly the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding portion of the polynucleotide sequence, which encodes the mature SRT polypeptides herein, is used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be

complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res., 6:3073 (1979); Cooney et al., Science, 241: 456 (1988); Dervan et al., Science, 251:1360 (1991)), thereby preventing transcription and the production of the SRT polypeptide. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into the SRT polypeptide (antisense - Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression (CRC Press: Boca Raton, FL, 1988). The oligonucleotides described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of the SRT polypeptide. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation-initiation site, e.g., between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

Potential antagonists include small molecules that bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the SRT polypeptide, thereby blocking the normal biological activity of the SRT polypeptide. Examples of small molecules include, but are not limited to, small peptides or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details see, e.g., Rossi, Current Biology, 4:469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details see, e.g., PCT publication No. WO 97/33551, *supra*.

These small molecules can be identified by any one or more of the screening assays discussed hereinabove and/or by any other screening techniques well known for those skilled in the art.

F. Anti-SRT Polypeptide Antibodies

The present invention further provides anti-SRT antibodies. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

1. Polyclonal Antibodies

The anti-SRT antibodies may comprise polyclonal antibodies. Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. The immunizing agent may include the SRT polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine

thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). The immunization protocol may be selected by one skilled in the art without undue experimentation.

2. Monoclonal Antibodies

The anti-SRT antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler and Milstein, Nature, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

The immunizing agent will typically include the SRT polypeptide or a fusion protein thereof. Generally, either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell [Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103]. Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies [Kozbor, J. Immunol., 133:3001 (1984); Brodeur et al., Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63].

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against SRT. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980).

After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods [Goding, supra]. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells

may be grown *in vivo* as ascites in a mammal.

The monoclonal antibodies secreted by the subclones may be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences [U.S. Patent No. 4,816,567; Morrison et al., supra] or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy chain. The heavy chain is truncated generally at any point in the Fc region so as to prevent heavy chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

In vitro methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques known in the art.

3. Human and Humanized Antibodies

The anti-SRT antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise

substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol., 2:593-596 (1992)].

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeyen et al., Science, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Human antibodies can also be produced using various techniques known in the art, including phage display libraries [Hoogenboom and Winter, J. Mol. Biol., 227:381 (1991); Marks et al., J. Mol. Biol., 222:581 (1991)]. The techniques of Cole et al. and Boerner et al. are also available for the preparation of human monoclonal antibodies (Cole et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985) and Boerner et al., J. Immunol., 147(1):86-95 (1991)]. Similarly, human antibodies can be made by introducing of human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in the following scientific publications: Marks *et al.*, Bio/Technology 10, 779-783 (1992); Lonberg *et al.*, Nature 368 856-859 (1994); Morrison, Nature 368, 812-13 (1994); Fishwild *et al.*, Nature Biotechnology 14, 845-51 (1996); Neuberger, Nature Biotechnology 14, 826 (1996); Lonberg and Huszar, Intern. Rev. Immunol. 13 65-93 (1995).

4. Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for the SRT, the other one is for any other antigen, and preferably for a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain

pairs, where the two heavy chains have different specificities [Milstein and Cuello, Nature, 305:537-539 (1983)]. Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker et al., EMBO J., 10:3655-3659 (1991).

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh et al., Methods in Enzymology, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. $F(ab')_2$ bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared can be prepared using chemical linkage. Brennan *et al.*, Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate $F(ab')_2$ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Fab' fragments may be directly recovered from *E. coli* and chemically coupled to form bispecific antibodies. Shalaby *et al.*, J. Exp. Med. 175:217-225 (1992) describe the production of a fully humanized bispecific antibody $F(ab')_2$ molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various technique for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny *et al.*, J. Immunol. 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger *et al.*, Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber *et al.*, J. Immunol. 152:5368 (1994).
Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt *et al.*, J. Immunol. 147:60 (1991).

Exemplary bispecific antibodies may bind to two different epitopes on a given SRT polypeptide herein. Alternatively, an anti-SRT polypeptide arm may be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD2, CD3, CD28, or B7), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular SRT polypeptide. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express a particular SRT polypeptide. These antibodies possess a SRT-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the SRT polypeptide and further binds tissue factor (TF).

5. Heteroconjugate Antibodies

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells [U.S. Patent No. 4,676,980], and for treatment of HIV infection [WO 91/00360; WO 92/200373; EP 03089]. It is contemplated that the antibodies may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

6. Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, *e.g.*, the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) may be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The

homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron *et al.*, J. Exp Med., 176: 1191-1195 (1992) and Shopes, J. Immunol., 148: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff *et al.* Cancer Research, 53: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson *et al.*, Anti-Cancer Drug Design, 3: 219-230 (1989).

7. Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (*e.g.*, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (*i.e.*, a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ^{212}Bi, ^{131}I, ^{131}In, ^{90}Y, and ^{186}Re.

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutareldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, Science, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

In another embodiment, the antibody may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (*e.g.*, avidin) that is conjugated to a cytotoxic agent (*e.g.*, a radionucleotide).

8. Immunoliposomes

The antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein *et al.*, Proc. Natl. Acad. Sci. USA, 82: 3688 (1985); Hwang *et al.*, Proc. Natl Acad. Sci. USA, 77: 4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent No.

5,013,556.

Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin *et al.*, J. Biol. Chem., 257: 286-288 (1982) via a disulfide-interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. See Gabizon *et al.*, J. National Cancer Inst., 81(19): 1484 (1989).

9. Pharmaceutical Compositions of Antibodies

Antibodies specifically binding a SRT polypeptide identified herein, as well as other molecules identified by the screening assays disclosed hereinbefore, can be administered for the treatment of various disorders in the form of pharmaceutical compositions.

If the SRT polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also be used to deliver the antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. See, *e.g.*, Marasco *et al.*, Proc. Natl. Acad. Sci. USA, 90: 7889-7893 (1993). The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, *supra*.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT ™ (injectable

microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

G. Uses for anti-SRT Antibodies

The anti-SRT antibodies of the invention have various utilities. For example, anti-SRT antibodies may be used in diagnostic assays for SRT, *e.g.*, detecting its expression in specific cells, tissues, or serum. Various diagnostic assay techniques known in the art may be used, such as competitive binding assays, direct or indirect sandwich assays and immunoprecipitation assays conducted in either heterogeneous or homogeneous phases [Zola, Monoclonal Antibodies: A Manual of Techniques, CRC Press, Inc. (1987) pp. 147-158]. The antibodies used in the diagnostic assays can be labeled with a detectable moiety. The detectable moiety should be capable of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety may be a radioisotope, such as ^{3}H, ^{14}C, ^{32}P, ^{35}S, or ^{125}I, a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin, or an enzyme, such as alkaline phosphatase, beta-galactosidase or horseradish peroxidase. Any method known in the art for conjugating the antibody to the detectable moiety may be employed, including those methods described by Hunter et al., Nature, 144:945 (1962); David et al., Biochemistry, 13:1014 (1974); Pain et al., J. Immunol. Meth., 40:219 (1981); and Nygren, J. Histochem. and Cytochem., 30:407 (1982).

Anti-SRT antibodies also are useful for the affinity purification of SRT from recombinant cell culture or natural sources. In this process, the antibodies against SRT are immobilized on a suitable support, such a Sephadex resin or filter paper, using methods well known in the art. The immobilized antibody then is contacted with a sample containing the SRT to be purified, and thereafter the support is washed with a suitable solvent that will remove substantially all the material in the sample except the SRT, which is bound to the immobilized antibody. Finally, the support is washed with another suitable solvent that will release the SRT from the antibody.

The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

EXAMPLES

Commercially available reagents referred to in the examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA.

EXAMPLE 1

Isolation of SRT cDNAs

1. Preparation of oligo dT primed cDNA library

mRNA was isolated from human tissue using reagents and protocols from Invitrogen, San Diego, CA (Fast Track 2). This RNA was used to generate an oligo dT primed cDNA library in the vector pRK5D using reagents and protocols from Life Technologies, Gaithersburg, MD (Super Script Plasmid System). In this procedure, the double stranded cDNA was sized to greater than 1000 bp and the SalI/NotI linkered cDNA was cloned into XhoI/NotI cleaved vector. pRK5D is a cloning vector that has an sp6 transcription initiation site followed by an SfiI restriction enzyme site preceding the XhoI/NotI cDNA cloning sites.

2. Preparation of random primed cDNA library

A secondary cDNA library was generated in order to preferentially represent the 5' ends of the primary cDNA clones. Sp6 RNA was generated from the primary library (described above), and this RNA was used to generate a random primed cDNA library in the vector pSST-AMY.0 using reagents and protocols from Life Technologies (Super Script Plasmid System, referenced above). In this procedure the double stranded cDNA was sized to 500-1000 bp, linkered with blunt to NotI adaptors, cleaved with SfiI, and cloned into SfiI/NotI cleaved vector. pSST-AMY.0 is a cloning vector that has a yeast alcohol dehydrogenase promoter preceding the cDNA cloning sites and the mouse amylase sequence (the mature sequence without the secretion signal) followed by the yeast alcohol dehydrogenase terminator, after the cloning sites. Thus, cDNAs cloned into this vector that are fused in frame with the amylase sequence will lead to the secretion of amylase from appropriately transfected yeast colonies.

3. Transformation and Detection

DNA from the library described in paragraph 2 above was chilled on ice to which was added electrocompetent DH10B bacteria (Life Technologies, 20 ml). The bacteria and vector mixture was then electroporated as recommended by the manufacturer. Subsequently, SOC media (Life Technologies, 1 ml) was added and the mixture was incubated at 37°C for 30 minutes. The transformants were then plated onto 20 standard 150 mm LB plates containing ampicillin and incubated for 16 hours (37°C). Positive colonies were scraped off the plates and the DNA was isolated from the bacterial pellet using standard protocols, e.g. CsCl-gradient. The purified DNA was then carried on to the yeast protocols below.

The yeast methods were divided into three categories: (1) Transformation of yeast with the plasmid/cDNA combined vector; (2) Detection and isolation of yeast clones secreting amylase; and (3) PCR

amplification of the insert directly from the yeast colony and purification of the DNA for sequencing and further analysis.

The yeast strain used was HD56-5A (ATCC-90785). This strain has the following genotype: MAT alpha, ura3-52, leu2-3, leu2-112, his3-11, his3-15, MAL^+, SUC^+, GAL^+. Preferably, yeast mutants can be employed that have deficient post-translational pathways. Such mutants may have translocation deficient alleles in *sec*71, *sec*72, *sec*62, with truncated *sec*71 being most preferred. Alternatively, antagonists (including antisense nucleotides and/or ligands) which interfere with the normal operation of these genes, other proteins implicated in this post translation pathway (e.g., SEC61p, SEC72p, SEC62p, SEC63p, TDJ1p or SSA1p-4p) or the complex formation of these proteins may also be preferably employed in combination with the amylase-expressing yeast.

Transformation was performed based on the protocol outlined by Gietz et al., Nucl. Acid. Res., 20:1425 (1992). Transformed cells were then inoculated from agar into YEPD complex media broth (100 ml) and grown overnight at 30°C. The YEPD broth was prepared as described in Kaiser et al., Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 207 (1994). The overnight culture was then diluted to about 2 x 10^6 cells/ml (approx. OD_{600}=0.1) into fresh YEPD broth (500 ml) and regrown to 1 x 10^7 cells/ml (approx. OD_{600}=0.4-0.5).

The cells were then harvested and prepared for transformation by transfer into GS3 rotor bottles in a Sorval GS3 rotor at 5,000 rpm for 5 minutes, the supernatant discarded, and then resuspended into sterile water, and centrifuged again in 50 ml falcon tubes at 3,500 rpm in a Beckman GS-6KR centrifuge. The supernatant was discarded and the cells were subsequently washed with LiAc/TE (10 ml, 10 mM Tris-HCl, 1 mM EDTA pH 7.5, 100 mM Li_2OOCCH_3), and resuspended into LiAc/TE (2.5 ml).

Transformation took place by mixing the prepared cells (100 μl) with freshly denatured single stranded salmon testes DNA (Lofstrand Labs, Gaithersburg, MD) and transforming DNA (1 μg, vol. < 10 μl) in microfuge tubes. The mixture was mixed briefly by vortexing, then 40% PEG/TE (600 μl, 40% polyethylene glycol-4000, 10 mM Tris-HCl, 1 mM EDTA, 100 mM Li_2OOCCH_3, pH 7.5) was added. This mixture was gently mixed and incubated at 30°C while agitating for 30 minutes. The cells were then heat shocked at 42°C for 15 minutes, and the reaction vessel centrifuged in a microfuge at 12,000 rpm for 5-10 seconds, decanted and resuspended into TE (500 μl, 10 mM Tris-HCl, 1 mM EDTA pH 7.5) followed by recentrifugation. The cells were then diluted into TE (1 ml) and aliquots (200 μl) were spread onto the selective media previously prepared in 150 mm growth plates (VWR).

Alternatively, instead of multiple small reactions, the transformation was performed using a single, large scale reaction, wherein reagent amounts were scaled up accordingly.

The selective media used was a synthetic complete dextrose agar lacking uracil (SCD-Ura) prepared as described in Kaiser et al., Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 208-210 (1994). Transformants were grown at 30°C for 2-3 days.

The detection of colonies secreting amylase was performed by including red starch in the selective growth media. Starch was coupled to the red dye (Reactive Red-120, Sigma) as per the procedure described by Biely et al., Anal. Biochem., 172:176-179 (1988). The coupled starch was incorporated into the SCD-Ura agar

plates at a final concentration of 0.15% (w/v), and was buffered with potassium phosphate to a pH of 7.0 (50-100 mM final concentration).

The positive colonies were picked and streaked across fresh selective media (onto 150 mm plates) in order to obtain well isolated and identifiable single colonies. Well isolated single colonies positive for amylase secretion were detected by direct incorporation of red starch into buffered SCD-Ura agar. Positive colonies were determined by their ability to break down starch resulting in a clear halo around the positive colony visualized directly.

4. Isolation of DNA by PCR Amplification

When a positive colony was isolated, a portion of it was picked by a toothpick and diluted into sterile water (30 μl) in a 96 well plate. At this time, the positive colonies were either frozen and stored for subsequent analysis or immediately amplified. An aliquot of cells (5 μl) was used as a template for the PCR reaction in a 25 μl volume containing: 0.5 μl Klentaq (Clontech, Palo Alto, CA); 4.0 μl 10 mM dNTP's (Perkin Elmer-Cetus); 2.5 μl Klentaq buffer (Clontech); 0.25 μl forward oligo 1; 0.25 μl reverse oligo 2; 12.5 μl distilled water. The sequence of the forward oligonucleotide 1 was:

5'-TGTAAAACGACGGCCAGTTAAATAGACCTGCAATTATTAATCT-3' (SEQ ID NO:563)

The sequence of reverse oligonucleotide 2 was:

5'-CAGGAAACAGCTATGACCACCTGCACACCTGCAAATCCATT-3' (SEQ ID NO:564)

PCR was then performed as follows:

a.		Denature	92°C,	5 minutes
b.	3 cycles of:	Denature	92°C,	30 seconds
		Anneal	59°C,	30 seconds
		Extend	72°C,	60 seconds
c.	3 cycles of:	Denature	92°C,	30 seconds
		Anneal	57°C,	30 seconds
		Extend	72°C,	60 seconds
d.	25 cycles of:	Denature	92°C,	30 seconds
		Anneal	55°C,	30 seconds
		Extend	72°C,	60 seconds
e.		Hold	4°C	

The underlined regions of the oligonucleotides disclosed above annealed to the ADH promoter region and the amylase region, respectively, and amplified a 307 bp region from vector pSST-AMY.0 when no insert was present. Typically, the first 18 nucleotides of the 5' end of these oligonucleotides contained annealing sites for the sequencing primers. Thus, the total product of the PCR reaction from an empty vector was 343 bp. However, signal sequence-fused cDNA resulted in considerably longer nucleotide sequences.

Following the PCR, an aliquot of the reaction (5 μl) was examined by agarose gel electrophoresis in a 1% agarose gel using a Tris-Borate-EDTA (TBE) buffering system as described by Sambrook et al., supra. Clones resulting in a single strong PCR product larger than 400 bp were further analyzed by DNA sequencing

after purification with a 96 Qiaquick PCR clean-up column (Qiagen Inc., Chatsworth, CA).

cDNA molecules isolated from this amylase screen are shown in Figures 1-562 (SEQ ID NOS:1-562, respectively), wherein the nucleotides "N" and "X" represent any nucleotide. The cDNA libraries from which these cDNA molecules were obtained are as follows:

(a) Human liver tissue

Figures 1-19, 124 and 130.

(b) Human placenta tissue

Figures 20-73.

(c) Human retina tissue

Figures 74-75, 81, 107-108, 139-140 and 340-341.

(d) Human salivary gland tissue

Figures 76-78.

(e) Human umbilical vein endothelial cells

Figures 79-80, 97, 110, 245-252, 254-260, 263-265, 413-421, 433-437, 444-449, 454-456, 462-467, 477-478, 480-485, 492-493, 515 and 548.

(f) Human thyroid tissue

Figures 82-84, 90-91, 96, 109, 141-143 and 268.

(g) Human small intestine tissue

Figures 85-86, 144-161 and 267.

(h) Human colon carcinoma tissue

Figure 87.

(i) Human lung endothelial cells

Figures 88 and 93-95.

(j) Human hypothalamus tissue

Figure 89.

(k) Human breast carcinoma tissue

Figures 92, 111-115, 206-213, 228-232, 269-270, 450-453, 534-547, 556 and 559.

(l) Human aortic endothelial cells

Figures 98-102, 125-129, 136-138, 216-217, 253, 261-262, 300-301, 327-330, 365-367 and 385-387.

(m) Human uterus tissue

Figures 103-106, 170-173, 176-183, 233-235, 238, 242-244, 266, 311-312 and 557.

(n) Human lung carcinoma tissue

Figures 106-108, 201-205, 221-227, 271-274, 334-339, 342-348, 350-351, 360-364, 372, 388-408, 411, 431-432, 479, 558 and 560-561.

(o) Human mammary epithelial cells

Figures 119-121, 214 and 316-320.

(p) Human chronic myelogenous leukemia tissue

Figures 122-123 and 131-135.

(q) Human spinal cord tissue

Figures 162, 167-169, 198-200, 236 and 315.

(r) Human fetal brain tissue

Figures 163-166, 174-175, 332-333, 422-430 and 494-502.

(s) Human fetal kidney tissue

Figures 184-197, 409-410 and 412.

(t) Human prostate tissue

Figures 215, 237, 239-241 and 349.

(u) Human mammary gland tissue

Figures 218-220, 275-276 and 331.

(v) Human adenocarcinoma tissue

Figures 277-299 and 302-310.

(w) Human fetal small intestine tissue

Figures 313-314.

(x) Human fetal lung tissue

Figures 321-326.

(y) Human testis tissue

Figures 352-359, 368-371, 377-384, 438-443, 457-461, 486-491, 513-514, 516-527 and 562.

(z) Human MCF-7 cells

Figures 373-376, 468-476, 503-512, 528-533 and 549-555.

EXAMPLE 2

Identification of full-length cDNA molecules

Oligonucleotide probes may be generated from the sequence of any of the SRT polynucleotide sequences disclosed herein, including those shown in Figures 1 to 562 and used to screen human cDNA libraries prepared as described in paragraph 1 of Example 1 above. The cloning vector may be pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science 253:1278-1280 (1991)), and the cDNA size cut may be less than 2800 bp. The oligonucleotides probes may be synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for SRT. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In order to screen several libraries for a full-length clone, DNA from the libraries may be screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, *supra*, with the PCR primer pair. A positive library may then be used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

EXAMPLE 3

Use of SRT polynucleotides as hybridization probes

The following method describes use of a nucleotide sequence encoding SRT as a hybridization probe.

DNA comprising the coding sequence of full-length or mature SRT is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of SRT) in human tissue cDNA libraries or human tissue genomic libraries.

Hybridization and washing of filters containing either library DNAs is performed under the following high stringency conditions. Hybridization of radiolabeled SRT-derived probe to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing of the filters is performed in an aqueous solution of 0.1x SSC and 0.1% SDS at 42°C.

DNAs having a desired sequence identity with the DNA encoding full-length native sequence SRT can then be identified using standard techniques known in the art.

EXAMPLE 4

Expression of SRT in *E. coli*

This example illustrates preparation of an unglycosylated form of SRT by recombinant expression in *E. coli*.

The DNA sequence encoding SRT is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from *E. coli*; see Bolivar et al., Gene, 2:95 (1977)) which contains genes for ampicillin and tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode for an antibiotic resistance gene, a trp promoter, a polyhis leader (including the first six STII codons, polyhis sequence, and enterokinase cleavage site), the SRT coding region, lambda transcriptional terminator, and an argU gene.

The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook et al., supra. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized SRT protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

SRT may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding SRT is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 fuhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an O.D.600 of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g $(NH_4)_2SO_4$, 0.71 g sodium citrate•2H2O, 1.07 g KCl, 5.36 g Difco yeast extract, 5.36 g Sheffield hycase SF in 500 mL water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM $MgSO_4$) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

E. coli paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A280 absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

Fractions containing the desired folded SRT polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

EXAMPLE 5

Expression of SRT in mammalian cells

This example illustrates preparation of a potentially glycosylated form of SRT by recombinant expression in mammalian cells.

The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the SRT DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the SRT DNA using ligation methods such as described in Sambrook et al., supra. The resulting vector is called pRK5-SRT.

In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 μg pRK5-SRT DNA is mixed with about 1 μg DNA encoding the VA RNA gene [Thimmappaya et al., Cell, 31:543 (1982)] and dissolved in 500 μl of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M $CaCl_2$. To this mixture is added, dropwise, 500 μl of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM $NaPO_4$, and a precipitate is allowed to form for 10 minutes at 25°C. The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 μCi/ml ^{35}S-cysteine and 200 μCi/ml ^{35}S-methionine. After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of SRT polypeptide. The cultures containing transfected cells may undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

In an alternative technique, SRT may be introduced into 293 cells transiently using the dextran sulfate method described by Somparyrac et al., Proc. Natl. Acad. Sci., 12:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700 μg pRK5-SRT DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5 μg/ml bovine insulin and 0.1 μg/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed SRT can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

In another embodiment, SRT can be expressed in CHO cells. The pRK5-SRT can be transfected into CHO cells using known reagents such as $CaPO_4$ or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as ^{35}S-methionine. After determining the presence of SRT polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed SRT can then be concentrated and purified by any selected method.

Epitope-tagged SRT may also be expressed in host CHO cells. The SRT may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged SRT insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 driven vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged SRT can then be concentrated and purified by any selected method, such as by Ni^{2+}-chelate affinity chromatography.

SRT may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e.g. extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or is a poly-His tagged form.

Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel et al., Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., Nucl. Acids Res. 24:9 (1774-1779 (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect® (Quiagen), Dosper® or Fugene® (Boehringer Mannheim). The cells are grown as described in Lucas et al., supra. Approximately 3 x 10^{-7} cells are frozen in an ampule for further growth and production as described below.

The ampules containing the plasmid DNA are thawed by placement into water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 mLs of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 mL of selective media (0.2 μm filtered PS20 with 5% 0.2 μm diafiltered fetal bovine serum). The cells are then aliquoted into a 100 mL spinner containing 90 mL of selective media. After 1-2 days, the cells are transferred into a 250 mL spinner filled with 150 mL selective growth medium and incubated at 37°C. After another 2-3 days, 250 mL, 500 mL and 2000 mL spinners are seeded with 3 x 10^5 cells/mL. The cell media is exchanged with fresh media by

centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at 1.2 x 10^6 cells/mL. On day 0, the cell number pH ie determined. On day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 mL of 500 g/L glucose and 0.6 mL of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability dropped below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22 μm filter. The filtrate was either stored at 4°C or immediately loaded onto columns for purification.

For the poly-His tagged constructs, the proteins are purified using a Ni-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows. The conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 μL of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

EXAMPLE 6

Expression of SRT in yeast

The following method describes recombinant expression of SRT in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of SRT from the ADH2/GAPDH promoter. DNA encoding SRT and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of SRT. For secretion, DNA encoding SRT can be cloned into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native SRT signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of SRT.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant SRT can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing SRT may further be purified using selected column chromatography resins.

EXAMPLE 7

Expression of SRT in baculovirus-infected insect cells

The following method describes recombinant expression of SRT in Baculovirus-infected insect cells.

The sequence coding for SRT is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding SRT or the desired portion of the coding sequence of SRT such as the sequence encoding the extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfecting the above plasmid and BaculoGold™ virus DNA (Pharmingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley et al., Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

Expressed poly-his tagged SRT can then be purified, for example, by Ni^{2+}-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et al. Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 7.9; 12.5 mM $MgCl_2$; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 μm filter. A Ni^{2+}-NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 mL, washed with 25 mL of water and equilibrated with 25 mL of loading buffer. The filtered cell extract is loaded onto the column at 0.5 mL per minute. The column is washed to baseline A_{280} with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching A_{280} baseline again, the column is developed with a 0 to 500 mM Imidazole gradient in the secondary wash buffer. One mL fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni^{2+}-NTA-conjugated to alkaline phosphatase (Qiagen). Fractions containing the eluted His_{10}-tagged SRT are pooled and dialyzed against loading buffer.

Alternatively, purification of the IgG tagged (or Fc tagged) SRT can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

EXAMPLE 8

Preparation of antibodies that bind SRT

This example illustrates preparation of monoclonal antibodies which can specifically bind SRT.

Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, supra. Immunogens that may be employed include purified SRT, fusion proteins containing SRT, and cells expressing recombinant SRT on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

Mice, such as Balb/c, are immunized with the SRT immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice by retro-orbital bleeding for testing in ELISA assays to detect anti-SRT antibodies.

After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of SRT. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against SRT. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against SRT is within the skill in the art.

The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-SRT monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

EXAMPLE 9

Purification of SRT polypeptides using specific antibodies

Native or recombinant SRT polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-SRT polypeptide, mature SRT polypeptide, or pre-SRT polypeptide is purified by immunoaffinity chromatography using antibodies specific for the SRT polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-SRT polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or

chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of SRT polypeptide by preparing a fraction from cells containing SRT polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble SRT polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble SRT polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of SRT polypeptide (*e.g.*, high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/SRT polypeptide binding (*e.g.*, a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and SRT polypeptide is collected.

EXAMPLE 10

Drug screening

This invention is particularly useful for screening compounds by using SRT polypeptides or binding fragment thereof in any of a variety of drug screening techniques. The SRT polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the SRT polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between SRT polypeptide or a fragment and the agent being tested. Alternatively, one can examine the diminution in complex formation between the SRT polypeptide and its target cell or target receptors caused by the agent being tested.

Thus, the present invention provides methods of screening for drugs or any other agents which can affect a SRT polypeptide-associated disease or disorder. These methods comprise contacting such an agent with an SRT polypeptide or fragment thereof and assaying (I) for the presence of a complex between the agent and the SRT polypeptide or fragment, or (ii) for the presence of a complex between the SRT polypeptide or fragment and the cell, by methods well known in the art. In such competitive binding assays, the SRT polypeptide or fragment is typically labeled. After suitable incubation, free SRT polypeptide or fragment is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular agent to bind to SRT polypeptide or to interfere with the SRT polypeptide/cell complex.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to a polypeptide and is described in detail in WO 84/03564, published on September 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. As applied to a SRT polypeptide, the peptide test compounds are reacted

with SRT polypeptide and washed. Bound SRT polypeptide is detected by methods well known in the art. Purified SRT polypeptide can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding SRT polypeptide specifically compete with a test compound for binding to SRT polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with SRT polypeptide.

EXAMPLE 11

Rational drug design

The goal of rational drug design is to produce structural analogs of biologically active polypeptide of interest (*i.e.*, a SRT polypeptide) or of small molecules with which they interact, *e.g.*, agonists, antagonists, or inhibitors. Any of these examples can be used to fashion drugs which are more active or stable forms of the SRT polypeptide or which enhance or interfere with the function of the SRT polypeptide *in vivo* (*c.f.*, Hodgson, Bio/Technology, 9: 19-21 (1991)).

In one approach, the three-dimensional structure of the SRT polypeptide, or of an SRT polypeptide-inhibitor complex, is determined by x-ray crystallography, by computer modeling or, most typically, by a combination of the two approaches. Both the shape and charges of the SRT polypeptide must be ascertained to elucidate the structure and to determine active site(s) of the molecule. Less often, useful information regarding the structure of the SRT polypeptide may be gained by modeling based on the structure of homologous proteins. In both cases, relevant structural information is used to design analogous SRT polypeptide-like molecules or to identify efficient inhibitors. Useful examples of rational drug design may include molecules which have improved activity or stability as shown by Braxton and Wells, Biochemistry, 31:7796-7801 (1992) or which act as inhibitors, agonists, or antagonists of native peptides as shown by Athauda *et al.*, J. Biochem., 113:742-746 (1993).

It is also possible to isolate a target-specific antibody, selected by functional assay, as described above, and then to solve its crystal structure. This approach, in principle, yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced peptides. The isolated peptides would then act as the pharmacore.

By virtue of the present invention, sufficient amounts of the SRT polypeptide may be made available to perform such analytical studies as X-ray crystallography. In addition, knowledge of the SRT polypeptide amino acid sequence provided herein will provide guidance to those employing computer modeling techniques in place of or in addition to x-ray crystallography.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80% nucleic acid sequence identity to (a) the DNA molecule of any one of Figure 1 to 562, or (b) the complement of the DNA molecule of (a).

2. The isolated nucleic acid molecule of Claim 1 comprising the nucleotide sequence shown in any one of Figure 1 to 562, or the complement thereof.

3. The isolated nucleic acid molecule of Claim 1 consisting essentially of a nucleotide sequence having at least about 80% nucleic acid sequence identity to (a) the DNA molecule of any one of Figure 1 to 562, or (b) the complement of the DNA molecule of (a).

4. The isolated nucleic acid molecule of Claim 1 consisting essentially of the nucleotide sequence shown in any one of Figure 1 to 562, or the complement thereof.

5. The isolated nucleic acid molecule of Claim 1 consisting of a nucleotide sequence having at least about 80% nucleic acid sequence identity to (a) the DNA molecule of any one of Figure 1 to 562, or (b) the complement of the DNA molecule of (a).

6. The isolated nucleic acid molecule of Claim 1 consisting of the nucleotide sequence shown in any one of Figure 1 to 562, or the complement thereof.

7. An isolated nucleic acid molecule which hybridizes to (a) the DNA molecule of any one of Figure 1 to 562, or (b) the complement of the DNA molecule of (a).

8. The isolated nucleic acid molecule of Claim 7 which hybridizes to the complement of the DNA molecule of any one of Figure 1 to 562.

9. The isolated nucleic acid molecule of Claim 7, wherein said hybridization occurs under stringent hybridization conditions.

10. An isolated nucleic acid molecule comprising at least about 10 consecutive nucleotides contained within (a) the DNA molecule of any one of Figure 1 to 562, or (b) the complement of the DNA molecule of (a).

11. The isolated nucleic acid molecule of Claim 10 comprising at least about 10 consecutive nucleotides contained within the complement of the DNA molecule of any one of Figure 1 to 562.

12. The isolated nucleic acid molecule of Claim 10 which is from about 10 to about 1000 nucleotides in length.

13. The isolated nucleic acid molecule of Claim 10 which is from about 10 to about 500 nucleotides in length.

14. The isolated nucleic acid molecule of Claim 10 which is from about 10 to about 100 nucleotides in length.

15. The isolated nucleic acid molecule of Claim 10 which is from about 10 to about 50 nucleotides in length.

16. The isolated nucleic acid molecule of Claim 11 which is fully complementary to the DNA molecule of any one of Figure 1 to 562.

17 The isolated nucleic acid molecule of Claim 10 which is detectably labeled.

18. A method of detecting the presence of a cDNA molecule which encodes a mammalian polypeptide in a mammalian cDNA library, said method comprising:

contacting said cDNA library with an oligonucleotide probe that hybridizes to the DNA molecule of any one of Figure 1 to 562, wherein said contacting is performed under conditions suitable for hybridization of said probe to a cDNA molecule in said library and wherein hybridization of said probe to a cDNA molecule in said library is indicative of the presence of cDNA molecule which encodes a mammalian polypeptide in said cDNA library.

19. The method of Claim 18, wherein said hybridization is performed under stringent hybridization conditions.

20. The method of Claim 18, wherein said oligonucleotide probe comprises at least about 10 consecutive nucleotides contained within the complement of the DNA molecule of any one of Figure 1 to 562.

21. The method of Claim 18, wherein said mammalian polypeptide is a human polypeptide.

22. A vector comprising the nucleic acid molecule of Claim 1.

23. The vector of Claim 22, wherein said nucleic acid molecule is operably linked to control sequences recognized by a host cell transformed with the vector.

24. A host cell comprising the vector of Claim 22.

25. The host cell of Claim 24, wherein said cell is a CHO cell.

26. The host cell of Claim 24, wherein said cell is an *E. coli*.

27. The host cell of Claim 24, wherein said cell is a yeast cell.

28. An isolated SRT polypeptide encoded by the nucleic acid molecule of Claim 1.

29. An antibody which binds to the isolated SRT polypeptide of Claim 28.

30. The antibody of Claim 29 which is a monoclonal antibody.

31. The antibody of Claim 29 which is a humanized antibody.

FIGURE 1

AGTTTGTTAAAAATAATAATGCCAATAATATATGTTATTTTACGTATGTTTATACAGATGCAC
GCTTATTTATACTTATGTGTAAGTGAAATAAATGGCAAAAATGATACAAGGCATAGGAAGAAG
AAATTAGGATTATATGCTATGTAAGAAGCAGTATAGTGTTTTTTGAAAATAGACTTGAATTAG
TTGGAAATCCATATTGAAAACTNTCGGGCAAACATTTTTAAAAAATAAAAAAATGATATGCTA
AGAAAGAAGAGAAAACGGAATTACACAAAATGNTCAATTAAAACCACAAAAGGAAGCAAAAGT
GTGGAAAACAAAAAGGGGAACAAAGAATAAGGCAACAAACAGAAAACAGTAACAAATATGGTA
AGCATTAATCCAACTATATTAATAATCACTTTAAATATCAATGGTNTAAATATGTCAATTATA
AGACAGAGATTACCAGAGTGGACACATTATATAAGCT

FIGURE 2

ACGTTCGCGGTTCGAGGTTAGGGCCCCGGAAGCCCGCAGTAATTNCACGTNTTCCCGCCCGNT
TCCGGCCCCCCAGTGCCGCCCTTCGCGGGCCGGAGGCGCGAGTCTGGGCTTTGGCGCCTTCGC
AGCCGCAGGCGACATCCTCTTTCCTAGCTAAAGCCCCAAACGCCCAGGTGGCTTCCTGGGAGA
GCACGGCTGAGCCTCCGCCTTCAGATCAGAACAGGCAGAGCCTCCAAGGGCGGCTTGGGCCCA
GTGCCTGCTTATCCTGCCCGTCTCTCCACACTTCTTCTTTCCCTGTCCGTTGGAGTCCATTCC
TTCCTGGAAAAGCCAAAGCCGCGCTCCCCTAAGAGTCATGTGTTACTGGATTAATTGAAATTC
TTGATAGGTAACAGAGTTTTATCATCAGCTTATGATTGCCTATGACTAGCTCAAAGTTAAGTT
TTAATAAACTAGTAAGTACAATAAACCTCATTCCTAAATACAAGGAAAAGAACTATATAATGA
ATACTTGTCTCTATGCCCCTCTCGCATAGATAACAATAATTTAGGTTTACCTTTAAATGAACT
GCATTTAAATGAAATTAATTTAAATGATTGTTTCACGGCACAGTTTCATCAATGGTCTACGGT
ATCCCTTATTTATGTATACATCAGTTTGTATACATCTGTATCTATGTATTTG

FIGURE 3

NAGAANGGAAGNGAAGGAGGAAGAGGNGNNNAAGAGGGAGGGGAAAAGNGGANGGNGNAGNNG
AGNANGGNGGNGGANNNNAGGNNGNAGNAGGNCCNAGANGGNAAGNGNTTGNAAGAAAGGGAN
NGCCNGGTAAAANAGNACCNNCCCAAGAAGNGATTANGGNGGNTTCCTNGNTGAAGGNTGTGG
ATCCCANNTNTTTCCCGGGANTTATNGNTNGGNAACAANATTTCNANGNGNNACNNAGGCAAA
CAATNAANTTNCCAAGGTNTTGGTAGNATTTCCCNCGGXXXXXXXXXXXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXXXNGATNTNGGGGTTTNTCCCCTTTCCCCTTCCCCTTTCCCCACCCCGGG
GGTTCNGGTTGGTNAAGAAAAAAAAAAAAAAAAAGAATTNTGGCGCGGCCTCGGCGGAGNTGG
TGATCGGCTGGTGCATANTCGGCNTCTTACTACTGGNTATTTTGGCATTCTGCTGGANANATG
TTNGTAAATACCAAAGTCGGCGGGAAAGNGAAGTTGTTTCCACCATAACAGCAATTTNTTTTT
TAGCAATTGCANTTATCACNTCAGCACTTGNACCAGAGGAAATATTTTNGGTTTCTTACATGN
AAAATCAAAATGGTACATTTAAGGANTGGGNTAATGNTAANGTCAGCAGACAGNTTGAGGACA
CTGTATTANACGGTTACTATACTTTATATTCTGTTATATTGTTCTGTGTGTTNTTCTGGATCC
CTTTTGTCTACTTATATTATGAAGAAAAGGATGATGATGATACTAGTAGATGTANTCAAATTA
AAACXXXXXXXXXXXX

FIGURE 4

AGTTTGTTAAAAATAATAATGCCAATAATATATGTTATTTAACGTATGTTTATAACAGATGCA
CGCTTATTTATACTTATGTGTAAGTGAAATAAATGGCAAAAATGATACAAGGCATAGGAAGAA
GAAATTAGGATTATATGCTATGTAAGAAGCAGTATAGTGTTTTTTGAAAATAGANTTGAATTA
GTTGGAAATCCATATTGAAAACTNTCGGGCAAACATTTTTAAAAAATAAAAAAATGATATGNT
AAGAAAGAAGAGAAAACGGAATTACACAAAATGCTCAATTAAAACCACAAAAGGAAGCAAAAG
TGTGGAAAACAAAAAGGGGNACAAAGAATNNGGCNACAAACNGCAAACAGTAACAATTNTGGT
AANCATTANTCCAATTATANTTNCNATTACTCTAAATATCAATGTTTTNAATATGTCTATTGT
NAGACNGAGNTTACCAGAGAGNACACATTATATAAGGTCNGANGNGTNGG

FIGURE 5

TTCNTTGTCAANNGTTTTTGGTTCCCCCTTNTTTCCNGGNTTNNTNTTTNGGAANAAAAATTT
NAAGNTATACCAAGNAAAAAATTAAATTCCAAGNATTGGATTGAATTCCCNGGGGATCTTNNA
GAGATCCCTTNGACTTTGACCNAAGGGTCCGGCTTTAGGGGAAGAAGTTGGTGTTTNGNTGGG
CCCTGGTACTGAAGACGCGTTCCGGGTAGCCCAAAGANGTTTCNTANTNACCCAAAGCCCCGC
ACCCGCCTTTTNTNTNTTTTCTTNTGGCAGGATGAGGCGTGCAGGCCTGGGTGAAGGAGTACT
TCCTGGNAANTATGGGAANTATGGNTATGNTAATAGTGGGTATAGTGCCTGTGAAGAAGAAAA
TGAGAGGCTCACTGAAAGTTTGAGAAGCAAAGTAACTGNTATAAAATNTNTTTCCCATTGAAA
TAGGCCATGAAGTTAAAACCCAGAATAAATNANNAGCGGANNNGGATTAAAAAGACGANTNNA
CAACNNTGATTTTGTANGTATAACTATGGGCATAANTGNAGATTTTTTCCAGANGGAGCTAAA
CAAAGATGTTGTGAGATATGNNGAGGNTATNATTAATTNTCAAGTTTGNTCACATAGGCGAGC
NTNAAAC

FIGURE 6

CCCCTTTTTCCNNGGTTTTTTTTTNGGAAAAAAATTTCAGGGGTANCCNGGGNAAAATTTAAA
NTCCAGGGTTTGGGGGGATTTCCCCGGGGTNCTTTTGGAGTTCCTTTGGACCTGNAACAAAGG
GTTGGAANTAAAANAAAAATTAAAAANCNGGGTTTTTNGGGGAAANTTNANAATGNGNTTGGG
GNCAAGAAAAATGGGTTTTTNGGGAGGGNAANGNNGGTTCATTTCCAAATNGNAGGGGGGNAA
AAATTTNAGGCTTNNGGGGNAGGNGGAAAAAAATTTCGTAGCCTCNAGGTTGNNATTTTTAAA
CCTNCAGAAGGTGGCCAGCCCCGNNTCANCNGNTGATNAAGGCAGATGGGAAAAGGGGGATAT
GGGGTNATAAGGGTACCTNTCACCCTTTTNGAAGGAAAAAAAGTGGTCCACAGNATTTTTGTT
TACCCAAGGGTAANANATGGAATTTTGTNGAANATAGGNGAATGGTGAGGCATTTGGAAANAN
GGGGGGGGTTTTTNTTGAANGGGGGAGTAGGGGTATGGTATTTTATGGGAAAANAGTTTTTT
GGCACTAAACCNTTTTGAATTACCTAATANATTTATGTGGAAACCTGTCCTTTTTTTNCAGNT
NAANAAAAATTTTTNCCCNTGAAANTNATTTTTAGNAAGNATATNAAAAGNATTTTTTTTTTC
AAGNGTCAGAAACCTTTTAGCATCATTGAAGTTAAAATGACTGTCCATAAACTTTTCAGAAAT
AGTAGGCATTTNAGGCNACNAGATTTGTANANGGNATNTTCATAGAATTATACCAGTGANTTN
ACCACCTGAANCCTCTTGGATCCCGTAAGCATTCTTTGCNACAAGGAAGGGAGGTATNCNGGG
TAANTCCTTGAANTTTTGGACNGGAACNATNACTTNGAATTTNAXXXXXXXXXXXXXXXXXXN
NGCCGCNGGGNCNTTTNTCGNGNN

FIGURE 7

NGNTTTNGTTCCCTTTTTTCCCNGGTTTTNTTTTTGGNAAAAAAATTTNAGGNTTAACCCAGG
NAAANATTAAATTCCAAGGGNTTTGGNNNGAATTCCCCGGGGGTTNCTTTTAGGGGTTCCTTT
GACNTTGAACCAAAGGTTTCNGGCCNGGAGGGGGGGGGGACCGGTTTTTTCCCCCNGCGTTTC
CCCCGGGGNTGGGGGTTGGGGNGCCCATTTGNNGAAGTNAGTGGGGAGGNGGANTGGGAACCC
GGNAGTTTTGGAGAAAGGNAGGTTCCTTCCTTAACCCTGGGGGTTCCNGGNGCCCNNGGAGNG
GCAGTTNGGGGAATANTGTTTNAGNGGTTNGGGGGGTTTTCCTNGGGTCCCGCCAAGGGGGNG
GTNCTTNATAAAAGGGTGCCTTTTTCCCCACAGNTTCCAGGTCNGAGAGGAGCCGCACCGTCG
GGTTGGAGATNGCGCGCAAGGNGGCTTNTGGTTNGGATTTGCCCCGCATCGGCCACAGGAAAA
GCCTGGTCCCTAGGCACGGTTGTGGTTCGAGCTTTTNGTTTTNTCGAACATTGAGGTATTCGC
TCAGCCCACCACGTTGTCNTCGGGGTTATTAGGCCCCAGTCACAAGCCCTATGATGTTTTCAG
ACTTCCCAGGTGGAGATAAGGAAAATTTTACTATTTCTGCAGAACTTCTGTTGATGTACAGCA
TTGTATTTAGCAACTTCTGTGTAGATCTGAAAATAAATACATTACCAATTGTTAGTTGCGTTT
TTATTAATATAATTTTAGAGNAGNNGANNNNGNTGTTAGACNTACNNAGGTAAATTATGTGGC
ACTTTNGCATTNTTGTTGNTNCATGTTCCCCTGNANTTTGCTTNGNGATTTCNATTTATTCCA
AANTCANNATAGAATGTAATTTCCNAACCCACAGTCCGXXXXXXXXXXXXNXXXXXXXXXXXX
XXXXXNN

FIGURE 8

GGANNNGNTTNCAAAATGGGATTTTTAACCAAANTANGGNAGAGAAAAGTTTAAGTGTTTTGC
CAAAAAAATTCCAAGGAAAATAANGCGGAGTTTGATTTTTCAGAGTTCAACAGGAAAAANGNG
AACAAANNGCCNGGAGNTTTNAAAGTTTTGGGAAAGCCANTTTTNATNTGTTCAAGGAACAGT
TTTTATTTGNGATGCCAATCAGAATTTTGGACCCAGTATAATCAAGGTCAGANTTTCAACCTA
AGCCTGGACCNGACCCATAATAACGGAAAGTTTAACAATGACTCACATTNTCNTAAAGTTTCC
AGCCAGAATAGGACACGNTCATTTGGTCATTTTCCCGGTCCAGAGTTNTTGGATGTAGAGAAA
ANTAGCTTTTCCCAGGAACAATTTTGTGATTCCGCAGGAGAAGGNTNTGAAAGAATACATCAA
GATTTTGAATTTGGTGATGAANTTAGCAGCAGCTCCACTGAACAGATAAGGGCAACCACACCT
CCAAATCAAGGAAGGCCAGATTNTCCTGTNTATGNTAACCTTNNAGAANTGNAAATNTCCCAG
TATGGTCTTCCCCCANTTCTTGGGAGCCTGGTAATTNAGNTTATTGGNGCNTGNGANACTNAT
ATAGACANCTNNNGGNGNTGTTANNATNANCACAGNGGGACATNGNATNGAAGTTGGNNACCT
CTTGCTTGGANTCGGGNXXXXXXXXXXXXXXXCNTCNCCGCNGGGNCNTTTNTNGNGNN

FIGURE 9

AGTTTGTTAAAAATAATAATGCCAATAATATATGTTATTTTACGTATGTTTATACAGATGCAC
GCTTATTTATACTTATGTGTAAGTGAAATAAATGGCAAAAATGATACAAGGCATAGGAAGAAG
AAATTAGGATTATATGCTATGTAAGAAGCAGTATAGTGTTTTTTGAAAATAGACTTGAATTAG
TTGGAAATCCATATTGAAAACTCTCGGGCAAACATTTTTAAAAAATAAAAAAATGATATGCTA
AGAAAGAAGAGAAAACGGAATTACACAAAATGCTCAATTAAAACCACAAAAGGAAGCAAAAGT
GTGGAAAACAAAAAGGGGAACAAAGAATAAGGCAACAAACAGAAAACAGTAACAAATATGGTA
AGCATTAATCCAACTATATTAATAATCACTTTAAATATCAATGGTCTAAATATGTCAATTATA
AGACAGAGATTACCAGAGTGGACACATTATATAAGCT

FIGURE 10

TTTTTTTTTTTTTTTTGAGACGGAGTCTTGCTCTGTTACCCAGGCGGAGTGCAGTGGCCA
TGATCTCGGCTCACTGCACTCCAGCCNGGATGACAGAATGAGACTCTGTCTCCAAAAATAAAA
TAAAATAAAATAAAAGTGATATGAACATAAAAGTACCTTAGGTCCAAACAATGATAACAACTA
ATATTTATTGGGCGCTTACTGTGGTATGCATTGTGTTAAGCATTTCACATGTATTTACTCATT
TAATCCTCACAACCATCCTAAAAGGTC

FIGURE 11

GTTCCACGTTGCTTGAAATTGAAAATCAAGATAAAAATGTTCACAATTAAGCTCCTTCTTTTT
ATTGTTCCTCTAGTTATTTCCTCCAGAATTGATCAAGACAATTCATCATTTGATTCTCTATCT
CCAGAGCCAAAATCAAGATTTGCTATGTTAGACGATGTAAAAATT

FIGURE 12

CGGAATTACTGTTCCAGCCGGCTCGGGTGGTTTTCCTTGCGTTCCCGCCACGNGGCGGCTCNT
CACTAAAAGGCTGCCCTTCTCCCCCACAGCTCCAGGTCCCNAGAGNNGCCGCACCGTCGGGTT
GGAGATCNCGCTCAAGGGTGNCCTCTGGGTCTNCATCTGCCCCNNCATCGGCCACAGGAAAAG
CCCTGGTCCCCTAGGCACGNTCGTGGTTCGAGCTTTTCGTTCTCTCGCACATTGAGGTATTCG
CTCAGCCCACCACGTTGTCCCTNCGGGGTTATTAGGCCCCAGTCACAAGCCNTATGGATGTTT
TCCAGACTTCCCAGGTGGAGATAAGGAAAATTTTACTATTTCTGCAGAACTTCTGTTGATGTA
CAGCCATTGTATTTAGCAACTTCGTGTAGATCTGAAAATAAATACATTACCAATTGTTAGTTG
CGTTTTTATTAATATAAATCTTAGAGTACTTGATTTTGCTGTTAGCTTTACTTAGGTAAATTA
TGTGGCACTCTAGCATTTTTGTTGTTGCATGTTCCATTGAACTTTGCTCTGTGTTTTCCATTT
ATTCCAAATTCAAAATAGACTGTAACTTCCCAATTTATTCTATGTTCC

FIGURE 13

AACGGACATAGCTCAGAGGGGTTAAGTGATCAGTGCAGGTTCACATAACTAAGTAATGACACA
GATGGGACCTGAACCTGGGTCTCAGGAGGCTCTGGTCCCTGGCCAAACTATGTGACTATGTAC
ATCCACCTGGTTTCTGCTCATGGGTTAGTGTGTGACAGGAACATTCCATGATGGCTGCAGCCT
CCATCCCAGGGGCACTTGGAGAAGCCATTCCACTCAGCCCCCTTGACCAGAAGAACCCTTGGG
ATGGAAAAGGGAATCCTGATTCTGCAACTACGTGCTCCCATGAGATCTGATTTTCAGCCAGGG
CTGATCCGTGGCTGCCAGCAAGGAAGCCACATCATCTCATTGTTACTAGACTGGCCCGGCTGA
AAGATTAGACAACAACGTTTACTTTGCCATTAGCCCTGCCTGGCACTCAGTATGGTATTGCCT
GGCTTTCAGGGGCACTGGTTACAGTGTCTCCGATGCAGGGCAGCCCCTGCCAAGGGCACAGGT
GTTCATAAATATTCCATGAACCAATCAAATCAGCCATGGAATGAGATCTAAGGAACCTATTCN
CGGCAAGCCTGAGACGAACACTTAAGCATGATAATGTTATCAACCTGGTCTGATAGGCATTGG
GGCACTGGTCCCTCGCATTTTCAATCAGGGTCTCACCCAGGGACNGATCTCCAACACCAAAAA
AACTTGGTTTTTCCATNCCCATTCCAAACTGGGCTCTCCNCCAAATGCCCTTAGGGCATTGGG
GGCAAGCTGGTCCCCTTGGCAGGTTTTTCATTCGAGGTTCTCACCCCCGGGGGACCGGGGAT
CTTCCAACACCNNNGGGGAACCTTGTGTTTTCCACTCCCCAGTCCCAGACGTGGGCTGCTTCT
CCAGAGATGCCCGCAGGTTTTAAAAGTTAAATTGATGATAACTTTTTTGGCTCAAGTATAGAA
GTAATACATTATCCATTGTAGATTATTTATAGGTAAATAAAATTTTTTAAATGACTTTTAACC
CCACTACCCAGAACTAACCACCACTGGNGGTAGTAAATGAATATATTGATTTACTTACAAATA
TAGGACCACAAGATATGGCACATGTTTTGCAACCAACCTGTTTTGATAGGCCCAGCTTGCTTC
TGCTGCGCTACTTTATTTGCAACCCAAACCCGCTTTTAAAAGAAAAATCATGGTCTTGTATTT
TACAAGTGAT

FIGURE 14

ATCGATTATAAAAGCAGAAATTTCACCTGGCTGCCCACCCCAATTTCAGTTTTCCTCTAAGAG
TTAGCCACTATTATCCCTTCAGAGTGGATATTCAGGCTTTTCTTTCCTGGCATGGACATACAT
ATGTAAATGTACATATATAAAAATAATTAGTGACACCATGCATGGTAGCTCACGCCTGTAATC
CCAGCACTTTGGGACGCTGAGGTGAGAGAATTGCTTGAGGCCATCAGTTTGAAGCTGCAGTGA
TCTATGATTGTGCCTCTACACTCCAGCCTGGGTGACAGGGTGAGACCCTGTCTCTTAAAAAAA
AATTCGTATTTGGGGTTAGTAGTAGTACCTACCTCATAGGTTATTATGGGATCAGTACAGTAG
GCCAGACAAAGTGCGTATGCTATTATTTTGCATGTAGTAAGTACCAGCATATACTACCTGTTA
TCCAGAAATTTGCTGAAATGTCCCTTGTATTTTCTCTCTTTCGATTTTGATCAGTCTTCCTAG
AAGTCATCAGTTTGAGTTTTTTCAAAGAACCAGTGGTTGGTTTAATGNATTTGGTTTGTTTTC
TTTTCCAANGATTTCTGCTTTACTCCTTAATAATTCCCTTTTCTGCTGGCTTTGGGTTCCATT
TGTTCTTCTGTCTCTTCTAGTTTCTTAAGGTAAAGGCTTAGATCATTGACTTCAGATTTTTTG
TCTTTTCTAACAAGTGTTCAAAACTATAATATAAATTTCCCTCTAAGCATTGTTTAGCCACAT
TTCACAAATTTGGAAATGTTTATTCATTTTCAC

FIGURE 15

TTTTATTAATTTATTTTTTTTTTAATACAGATTTTCCAGTGAGGGGCTTTTTCAACCCCATT
GGTTCTATTTTCTTGTATTTTTCCATTTAATTTGCTTCATAACTTAAACCAAGTCTCTTCTAG
TCTTAGGTATTATTTCTCGATTTTGTGCTGATGGGCATGTTTATAAGAACTGGAGAGGTGATT
TATTGGAATGAACTAACTGACTTCCTCCATTCCCCTCTTCCTTTTTGACATGAATTTTACTAC
TTCACAAATGAAGAATGATGTTATGAAGTTACCGTGGCAAAG

FIGURE 16

CCCACGCGCCGCTAACCCAATGTTCTTTTTTAGAATTTCAGGTTGTGGCATCCACTGAGTATG
CAGCTACTATGGTTTTTGTATGGGACGTATAAATACTTGATTATATACGACAGATTTTAATGT
CTTTAAAGACTTCCTGCTGTATTAACATATTGTAATGGAGTCTTTTAAATACTAGGTTGAATT
TAATTGAAGTCACACACATCTTGAAGTGGTAACTGCATAGTAAATACTACCAAGAGTTTTTTT
CACGTGGGAGTATCCTAAAACTCTGCCATGGGTGTAAATGTTTTACATTAATTTCATAATTGG
ACAGACCCTGCATTTAGCGAAAACATTTTGTTTTGAAAGTGTGTTCTTTTTGTCGCACTGTTA
CTGCGTAACACTTCTCAACATTCTGTAAGTTAAATTATTTTAAAATAACTATGGTGAATTCAT
GTTTATTTTTTTTTACTTTGAAAATTGTAGTACTCAGGTGGTATTTAATGGGAAAGGATCCTT
TGGGTATAAA

FIGURE 17

AATGTCCTTTTTTAGGAATTCCAGGTTNTGGCATCCACGGGGGTTGCCGCCTACTANGGNTTT
TGTAAGGGGACCGTATAAATAACTGGATTATATNCGACAGATTTTTAATGTCTTTAAAGACTT
CCTGCTGTATTAACATATTGTAATGGATCTTTTAAATACTAGGTTGAATTTAATTGAAGTCAC
ACACATCTTGAAGTGGTAACTGCATAGTAAATACTACCAAGAGTTTTTTTCACGTGGGAGTAT
CCTAAAACTCTGCCATGGGTGTAAATGTTTTACATTAATTTCATAATTGGACAGACCCTGCAT
TTAGCGAAAACATTTTGTTTTGAAAGTGTGTTCTTTTTGTCGCACTGTTACTGCGTAACACTT
CTCAACATTCTGTAAGTTAAATTATTTTAAAATAACTATGGTGAATTCATGTTTATTTTTTTT
TACTTTGAAAATTGTAGTACTCAGGTGGTATTTAATGGGAAAGGATCCTTTGGGTATAAA

FIGURE 18

CTTCATAACTTAAACCAAGTCTCTTCNAGTCTTAGGTATTANTTCTCGATTTTGTGNTGATGG
GCATGTTTATAAGAACTGGAGAGGTAATTTATTGGAATGAACTAACTGACTTCCTCCATTCCC
CTCTTCCTTTTTGACATGAATTTTACTACTTCACAAATGAAGAATGATGTTATGAAGTTACCG
TGGCAAAG

FIGURE 19

TGGGGCCCCCCCAACCCCGGCNGGTATCCAAGGAAAAAATTTTTTATTATGGGGTTTCCNGGA
ACTATTTGGGNCCTATGGAAATAGCCCTTAAAGNGCTTACATTCATGNGCTACTTTAACATGA
ATGGAGAAAATCCGTTTATGGAAGTACAGTGACAATTGNCCCAATCACTCTGTCCATCAAACC
ACTCAGGCTAGTTTGTACNAGTAGAGTTTTGNTTCNANTTTTATTTTTATTAATTTTATTTTT
TTTTTAATACAGATTTTCAGTGAGGGGCTTTTTCAACCCCATTGGTTCTATTTTCTTGTATTT
TTCCATTTAATTTGCTTCATAACTTAAACCAAGTCTCTTCNAGTCTTAGGTATTANTTCTCGA
TTTTGTGCTGATGGGCATGNTTATAAGAACTGGAGAGGTAATTTATTGGAATGAACTAACTGA
CTTCCTCCATTCCCCTCTTCCTTTTTGACATGAATTTTACTACTTCACAAATGAAGAATGATG
TTATGAAGTTACCGTGGCAAAG

FIGURE 20

CAGCTCCGGAAGACTATGCACCCAAGCACCAAACTTCCANCCAGAGAGAGAGACGTCCTCCGA
TAACAAAAATCCTTGCTTCCTCTGTCTGTGACTTTACACNCAGTTGTTCAAAGTTGTTAAANG
NCAAGAGTCAATCACATCCCTAGGACTACCTCCCAACTCTCCTGACTCTTATGTTATTGAAAA
AACAAACAAACAAANACTCCTTTATGATGNTATTCAACTTGAGTGGGGTTTTTTTTTCCACTT
TGGTCCTGGATATAATGAAATGATACATATTAGGATAAATTTTCACTGTGTATAGTAGCAATA
CGAACACACATGCCAATGTATCAACATATCTACTTGGTTACATTTTGGTTTATGATAATCGANN

FIGURE 21

TGGAATAACTGGAAATTTATTGGATCCAGGTTCCACATTGGCAGTTTGGAAACTACTACCAAA
AAGATTTCACCAATTTACAACTCCATCATTAGTAAGAANGCCTGTTTGCCTATAGTCTGCCAA
CCTGAACCCTTAAAAATTTTTGCCAANCTGGTAGGCAAAANTCTTTCTTTTCTTTGAATATTA
ATGAGGAGGAACATCTTTTCATGTTTCTTGGCCATTTGCANTTCCTATTATGAATTGCTTCNG
GCCCATTTTCCTTTTTTTAATTATGAAAGTCTAATGACTACCTTCTCATTGTATAAAAAACAC
AGTTCTTTGAATAGAGAGACCCTTTTCTCCAATGCTACCAATCACATTCCACTTACCACAGTT
TAACATACATCCTCTAGTCACCTTTCCCGA

FIGURE 22

TAGGGTCCTATTGGTTGCCTAAGCATACTTNTTAACTTGTGCCATTGGCCTTTACTTTTATGG
AGTTTTCAGGAAACTATTTTATANCATCTAGTTATTTAGTCTACGTATCTCTATTTAGTGGAG
CCTTTTCCCCTCAAATAATATATTTTATCATTTTTGGACTTATATAAANCATAATTAAATAAA
TTTTTTCTTAATACTGTTGGACTTTGTATATACAAGTTCAGATAACTTTTTCGAAGATAGTTT
CTTATATAAANGTAATTTAATTTTTTTTACTCTTCTATACAGTTNNTTAGATGTAAAGGAATT
AGCACAATCTCTGGCAGTTTTATAAAAGCTGTTGAAGCTCTTGTCCTGCACTGTCTTTAGGTA
TCATAGGTATCAGGTTTGCTTTGTGTTAATGCCACTTCAAGTCATTATTTGGTTTCTGCTATT
TTTTTACCTGAG

FIGURE 23

ATACATATATATGTGTGTGTGTGTGTGTGTGTATGTATANATNTAATCATTTACACTCTTT
TGGGGGTCAAGAATTTGAATGAAGAAAAACAAATCCAATTAATTTTGGCTTCCAGTTACTTCT
GATAAAATCAGTGAAGGTTCTTGGATTTTGAAATCTCAGTTGTGCATTGCTTTTTTTAGATCC
TGCCAGGTTACNNTTTTTTAAATAACATGTACAAATTCATCTTTTTCAGTATAGACTATTGTA
AGTTTTTGGAAATTGTTATAGTCATAGAACCATGATCACTAACAAGATATATTCCCCCACTCC
AAAGTCCTATGTGTTCCTTTTGTAGTTAACCTGTCACCCAC

FIGURE 24

ACCCTTGACCCAACGCGGCCCCCCGACCGNTTCATGGCCAAACGCGGGNCTCCAGCTGTTGGG
CTTCATTCTCCCCTTCCTGGGATGGACCGGCGCCCATCNTCAGCACTGCCCTGCCCCAGTGGA
GGATTTACTCCTATNCCGGCNACAACATCGTGACCGCCCAGGCCNTGTACGAGGGGCTGTGGA
TGTCCTGCGTGTCGCAGAGCACCGGGCAGATCCAGTGCAAAGTCTTTGACTCCCTTGCTGAAT
CTGAGCAGCACATTGCAAGCAACCCGTGCCTTGATGGTGGTTGGCATCCTCCTGGGAGTGATA
GCAATCTTNNTGGCCACCGTTGTNNNTGAAGTGTATGAAGTGCTTGGAAGACGATGAGGTGCA
GAAGATGAGGATGGCTGTCATTGGGGGCGCGATATTTCTTCTTGCAGGTCTGGCTATTTTAGT
TGCCACAGCATGGTATGGCAATAGAATCGTTCAAGAATTCTATGACCCTATGACCGA

FIGURE 25

TTTTCTTTTTTCTCTTTTTTAAATTACCTTTGTTTTGCGGTAAGGAGTTGGGGAATTTGTGGT
GGCAGGGAAGTAATGTAAGTTGCTTTATAACTCACTGTCTAACAAAGTTTTGAAAATTTGTCT
GATATGTAATTAGGTACTTTAGGGTTATTAGGTTTTCATAAAAATTCTGGTTAGGGCTCTTGC
CCTGCTCCCAATGAAAGCCTTTCCACAGGGCAAATATAAAAGAGAGAGTAGAGGGAATCCCCC
TGAGGTTTAAATAAGTCAAACCAGTAAGTAATAGTGCTAAGTTTGTCAGTGNCCTCTCTTTCT
TACTGTACTTAACATCTAAAGGGCACCTCATTTATTTTCAGCTAATTATGTTCTTTATGAGTG
ACTGTCAAATCAGGGAAGGGTGTGACGATCATGTGGAGATACCTTTTCTAATTAATAGCTGCC
TTGCTCCTCAAGATTCTGACGAACC

FIGURE 26

CTTCTTGACACTGCCCTTTCCCTTCCCCCNTCCCANCCTGCCCGACCCATGCCCGCGGGCGTG
CCCANGTCCCACCNTACTTGAAAAATGTTCGCCAGCCAGTCTCCTTGGCCCATGTNCGCAGGG
GCAGAAGTGGTGCCACAGGTACTACCGACCGGACCTGACAATACCTGAAATTCCCACCAAAGC
GTGGAGAACTCAAAACGGAGCTTTTGGGACTGAAAGAAAGAAAACNCAAACCTCAAGTNTNNN
CAACAGGAGGAACTTAAATAACTACGTCCAAGAATTCTGTGAATAATATAAGTCTTAAATATG
TATTTCTTAATTTATTGCATCAAACTACTTGTCCTTAAGCACTTAGTCTAATGCTAACTGCAA
GAGGAGGTGCTCAGTGGATGTTTAGCCGCGA

FIGURE 27

CGTGAAACACCCCTTTATTTCCTTCATAACTACTCANTATGNCTATTTCCTTCACCAGATGNA
AGCTCCTGAGCTCAGNCNCTGACTGTCTTTTTCAACACTGACTAGTACATAACAGGCACCCAA
TANTTNNTTAATTGTGGTAAAATATACATAACAAAGTTACCATTTTAAGNATNTAATTCAGCA
GCGTTACATACATTCAAATTGTTGTGCAACCATCACCACNNTCCATCTCCGGAACTTTNTATC
TTCCCAAGCTAAGGCTCTTGGCCCATTAAACAATAACTTCTAATTGCACCCTTCCCTGTCCAC
CCTGGTGACCATCATTCTGCACTCTATGAATTTGGCTACTTTATGTCCCCCAAATAAGTNGAA
TCATACCGACCC

FIGURE 28

TGGCATGTGGGCCCATTTCAGTTTCCCTACATGTTCCCAAAANTTATTTAAATTACTGTGTCC
AAAATTATGAGGACAGTGTCATTCATTCACCATAGTTTATANTCTTAGTTANATATCAAACTT
CCTTGGCACCTAGGATAAGAACATTTCTTTTGAAGTTATCCAATTTTTTTTATTTTTACTTG
ACTTGAAGGAAAGTTGGAAAATATGGTGGAAAAAATCTTCCGCATTAAAAGGGTCNNTAAAAC
ACAACCATTTACGATCTCAGTCAGCAGATTTACTCTACTCAAGGAAAAAAAGAAACAATCTTA
TTGGAAGCAGATGTTGACACTGTGTCAGTTATTGAAGACGGAAGGAGTTCACTTGAGCCATTG
CAGTTACAAAGGGGTATTGATCGA

FIGURE 29

TCTGCCCCTGAAATATACAAGGGTCATGCCCAAATTAANACAGGTTNACCTTTGTAGAGGTAA
ATATGTTGGCATTATTTATTGACATTTATGCTTCAAGCATGTCTTATTNTATGTAATTTTAAG
AAATACTNTATTTAANTNGTGANATATACCTAAAAGCATACTAGTTAGCTNTTAGANTCTCAC
TTAGGGAGGGTAAAGAAACATCACTGATGCCAATATGAAGATTTNTAAACAAATCCTTTGTNT
AGAANTTTTTTCTTTTCGTGCACCTCACAACACANTTACCATCGNACC

FIGURE 30

GGCCGGTTCTTTTAAGATCTTTGACCTGANCCAAAGTTTCGGGGAAGGGGGGGTTGCCCAGGT
GGAGTGCATGGGGGATTTTGGNTTAATGCAAGTTCCCCTTCCNGTGTTAANGCCATTTTCCTG
CTTCAGCTTTTTTGAGTAGNTGGAAANACAGGCGCCCGCCAANACACCTGGNTAATTTTTTGT
ATTTTCAGTAGAGACGGGGTTTCACCGTGGTTTCAATNTCCNGACNTTGTGATCCGCCCGCCT
NGGNTTGCCAAAGTGNTGGGATTATAAGCGTGAGCCACCGCGCCCGGCCGAGATGTTTTGATA
CAGGCATGCAATGTGAAATAATCAGATNATAGACAATGAGGTATCCATCCCCTCGAANTTTTA
TCCTTTGTGTTACTAACAATCCCGTGAACACTTTTTTAGTTATTTTAAAATGTATAATTAGTT
ANTACTGACTATAGTCAACCCTGTTATGCTGTCAAATAATAGATNTTATTCATTCTTACTGTT
TTTTTTGTACTCATTAACTGTTCTCANCGCCGAACC

FIGURE 31

GTTTTTTTTTTTTGAAGCGAACTTTTGCTATATTGCTAAGGCTAGTTTTGAACTCNTGGGNTC
AAGCAATACTGCCTTGACCTCCTAAAGTGCTTGGATTACAGGCATGAGNTACTGCGCCTGGCC
TGCAATATGTATTTTAAGCTACTTTTTTNTTATTCCGNACC

FIGURE 32

TGTCGACGCGAATGCCCCGCGGGCGGAGAACTGGGCTCCCACCGAGGAGGCTGGAGGCAGGTT
CGCTGTGGTTCCCCCTCCCGACCTGGCAGAGCTGNCGGGAGCTCTCTGAGGTCCNTCGAGAGT
ACCGGAAGGAGCACCAGACTACGTGTTCCCTGCTCTTCTGCGGCGCCTACCTCTACAAACAGG
GCTTTGCCATCCCCGGCTCCAGCTTCCTGAAGTTTTAGCTGGTGCCCTTGTTTGGGCCCATGG
CTGGGGCTTCTGCTGTGCTGTGTGTTGACCTCGGTGGGTGCCACATGCTGCTACCTGCTCTCC
AGTATTTTTGGCAAACAGTTGGTGGTGTCCTACTTTCCTGATAAAGTGGCCCTGCTGCAGAGA
AAGGTGGAGGAGAACAGAAACAGCTTGTTTTTTTTCTTATTGTTTTTGAGACTTTTCCCCATG
ACACCAAACTGGTTCTTGAACCTCTCGGCCCCAATTCTGAACATTCCCATCGTGCAGTTCTTN
TTCTCAGTNCTTATCGGTTTGATCCCCGGA

FIGURE 33

AAAAAAAAAAAAAAACTGCCTTTCTTCCCCTCAGTCAACTTTTGTGCTCCAGAAAATTTTCTAT
TCTGTAAGTCTGAGCGTAAAACTTCAGTATTAAAATAATTTGTACATGTAGAGAGAAAAATGA
CTTTTTCAAAAATATACAGGGGCAGCTGCCAAATTGATGTATTATATATTGTGGTTTCTGTTT
CTTGAAAGAATTTTTTTCGTTATTTTTACATCTAACAAAGTAAAAAAATTAAAAAGAGGGTAA
GAAACGATTCCGGTGGGATGATTTTAACATGCAAAATGTCCCTGGGGGTTTCTTCTTTGCTTG
CTTTCTTCCTCCTTACCCTACCCCCCACTCACACACACACACACAC

FIGURE 34

ACCCGGCATTAGGGAGGCGAGGTGNGCAATGTCTTAACCCCGGGCTCAACCAGTCCTCCGGCT
TCTGCTTCCCAAGGTGTNGGGATTGCCAGGCTGGAGCCCATTGNGCCCAGTCTATTGTATAGT
TTTAAAAAAACAAAACCAAAAGGCTAATAAATGGCACCCCTTTGCAAGCTCTTCCCCCTCCCT
TTCTTTTTCCTTCCCAGTGTCTCCTACTTCTCTGACCTAGTTGACAGCATTATACTTTTGGAT
GTTGGTAGCATGTATAAAGTACATTATTACATAACAAGTTAATATAACATAATAGTTTCAAGG
GTTTTGCCACTTAATTATACTAAGTTACTTAACCTCTCAATNCCTTATCTGTAGATTTTGTTT
TTGATAGGGTGGGATAGTAATAGTAACTACAAGGTTTCACAAGGTTGTGAAATTGAATGAGAA
ATACATGGCACTTTAACAAGTCACTATGGATTATTTAATTTCTTTTCTTCTTCTTCTGCTGCT
GCTTCTCCC

FIGURE 35

ACTATGGTAAATAGTTATACTGTATTGGTTTAGGAAATAATGGCCATTTTTAAAAGTCTGTAC
ATGTTCAGTACAGACACAGTCTTTTTGAAGTATTTTTTATCCCTCCTTTGTTGAATCCCATGG
ATGCAGAACCATGGATATGAAGGGCTGACTATATTCTCACAGTTATATTCAAGTTGTATTTTG
AATGATTTTATGACAATCTTTTACCAAAGGGCCAACTGTATTCTCATGTTTATTATTCAAGTT
GTATGACAATTTCATATCAGCCCCCCAGAGAGTTGGCATTTGGATTGAAATCATACTGAGTCT
CTAGATTAATTTAGGGAGAAGTGACATCTTTATAATTTTGAATCTTCCTATCCATGTATATGC
GAGTGTTTTGTATTTCAGTGGCATTTTCAAATTTTCTTCAGGTAGGTCTCTTAGTGTTTATTC
CCGA

FIGURE 36

ATTCTCCCCTCCTGGATGGATCGCNCCACCGTCACATTGCCTTCCCCCANTGGAGGATTNACT
CCTATGCTGGCGACAACATCGTGACCCCCCAGGCCATTTACCGAGGGGCTTTGGATGTCNTGC
NTGTCGCAGAGCACCGGGCAGATCCCAGTGCAAAGTCTTTGACTCCTTGCTGAATCTGAGCAG
CACATTGCAAGCAACCCGTGCCTTGATGGGGTTGGCATCCTCCTGGGAGTGATAGCAACCTTT
GTGGCCACCGTTGGCATGAAGTGTATGAAGTGCTTGGAAGACGATGAGGTGCCAGAAGATGAG
GATGGCTGTCATTGGGGGCGCGATATTTCTTGTTGCAGGTCTGGCTATTTTAGTNGCCACAGC
ATGGTATGGCAATAGANTNNTTCNNGNNNTCTATGACCCTATGACCCCAGTCAATGCCAGGTA
CGAATTTGGTCAGGCTCTCTTCACTGGCTGGGCTGCTGCTTCTCTCTGCCTTCTGGGAGGTGC
CCTACTTTGCTGTTCCTGTCCC

FIGURE 37

TTTTTTTTCTTGTTTAAGCTGACTCTTTGCTCTAATTTTGGAAAAAAAGAAATGTGAAGGGTC
AACTCCCACGTATGTGGTTATCTGTGAAAGTTGCACAGCGTGGCTTTTCCTAAACTGGTGTTT
TTCCCCCGCATTTGGTGGATTTTTTATTATTATTCAAAAACATAACTGAGTTTTTTAAAAGAG
GAGAAAATTTATATCTGGGTTAAGTGTTTANCATATATATGGGTACTTTGTAATATCTAAAAA
CTTAGAAACGGAAATGGAATCCTGCTCACAAAATCACTTTAAGATCTTTTCGAAGCTGTTAAT
TTTTCTTAGTGTTGTGGACACTGCAGACTTGTCCAGTGCTCCCACGGCCTGTACGGACAC

FIGURE 38

CCCAACTTGGAGGTGGAGACTATGGAGNTGATCGGATGGGCCCGGGGCAGACTTTCCCCTTGG
NGCTGTTCTCGTGATAGTGAATAAGGCTCACCAGATCAGGTTTAAAAGTGTGTAGCCTCCCCA
TTCTCTCTCTTCCTCATCCAGCCATGTAAGACNTGCCTGCTTCCCCCTCACCTTCTGCCAGGG
TTGTAAGTTTTCTGAGGCCTCCCAGCCATGCTTCCCTGTACAGCCTGTAGAACCATGAGCCAA
TTAAACCTATTTTCTTTATAAATTATCCAGTCTCAGGCATTTCTTTATAGCAGTGTGAGAGTG
GACTAATAGAGCTAGTTATTAGTAGAGCCAAGATTTAAATTCGAGCTTGCTGGCTCCCGAGTT
CTACTTTCTCAAACCCTATGTTAAGCTATTGTCCACAGCATTCAACATTGTTGAATTATCTTT
GTCAACTAACCTTGGAAGTCTTAAATTTTGTCCTAATCCTGTCCCCTATTCC

FIGURE 39

TTTTTTTTTTTTTTTTCTTTTGTACTGAGCTCAGCATAGACTAATACTACCTTAATGTTAAAA
TCTGAATTTCTTTTAGCATTTTGCTTAAAAGCAATATGCTATTTGCTTATTCCGTGCGAA

FIGURE 40

TTTTTTTTTTTTTTTTTCTTTTGTACTGAGCTCAGCATAGACTAATACTACCTTAATGTTAAAA
TCTGAATTTCTTTTAGCATTTTGCTTAAAAGCAATATGCTATTTGCTTATTCCGTG

FIGURE 41

AGAGCACCGGCAGATCCCAGTNCAAAGTCTTTGACCCTTGCTGAATCTGAGCAGCACATTNCA
AGCAACCCCTTGCCTTGAAGGTGGTTGNCATCCCCCCTGGGAGTGAATAGCAATCTTTGTGGC
CACCGTTGGCATGAAGTNTATGAAGTGCTTGGAAGACGATGAGGTGCAGAAGATGAGGATGGC
TGTCATTGGGGGCGCGATATTTCTTCTTGCAGGTCTGGCTATTTTAGTNNCCACAGCATGGTA
TGGCAATAGNATNNTTCGNGGNTTCTATGACCCTATGACCCCAGTCAATGCCAGGTACGAATT
TGGTCAGGCTCTCTTCACTGGCTGGGCTGCTGCTTCTCTCTGCCTTCTGGGAGGTGCCCTACT
TTGCTGTTCCTGTCCCCGAA

FIGURE 42

AGGTAGTCCTTAAAAAAAAGTCTCCTCTCTGTACCCTTCTTCACCCAATCTACAACTAGGTTT
TTTGGTAGGAATTTTATTATTAGNTACCAAACANGGTAACATCTTTACATGCCAGATTCCAAA
GATACCCTAGAAGAGCCAGAGGGTTGCACTTCCTCTCTCTCACTTTGCATTCCCTCCTAAGAA
ATACTTGCCCCTAACTCAAAGGGCAGAAGGAGTCCAGGGCTCTTTCAGCATTAAAATTCTCTA
TAGTTTTCTGGGAGAGGCACATGTTCTGAGTGTGAGGAGAACTGTTCTGGTTATTGTTTATAA
ATTGTTTTCATCTTCTATTTCTTATAACAGATTATAAATTTATGTTTTCTGATGCTTCATACT
ATTATGAGGATTTGGTTGGCAAATTATCTTACAATAACCACCCATATATTCATGCATGG

FIGURE 43

CCACCAAGAGCCTGAAGGCAGTCNCTGTGTTCCCCTTCCGACCTGGCAGAGCTGCGGGAGCTC
TCTGAGGTCCTTCGAGANTACCGGAAGGANCACCAGGCCTACGTGTTCCTGCTCTTCTGCGGC
GCCTACCTCTACAAACAGGGCTTNGCCATCCCCGGCTCCAGCTTCCTGAATGTTTTAGCTGGT
GCTTGTTTGGGCCATGGCTGGGGCTTCTGCTGTGCTGTGTGTTGACCTCGGTGGGTGCCACAT
GCTGCTACCTGCTCTCCAGTATTTTTGGCAAACAGTTGGTGGTGTCCTACTTTCCTGATAAAG
TGGCCCTGCTGCAGAGAAAGGTGGNGGAGAACAGAAACAGCTTGTTTTTTTTCTTATTGTTTT
TGAGACTTTTCCCCATGACACCAAACTGGTTCTTGAACCTCTCGGCCCCAATTCTGAACATTC
CCATCGTGCAGTTCTTCTTCTCAGTTCTTATCGGTTTGATCCCATATAATTTCATCGA

FIGURE 44

GGGTTTTCCAGGACTCCCCCCNACCCCCGGCCACTCNACTGGTGGAAATGCCTCTGCCCAATA
GACTTGCTGTCCTAACCCTCGTTTAGGACTTCTCATTTACTGCAGATATTGGTACACATAGGT
AGTGGGCGGCTGCCTGAGAGAGACCATTTGGTACTTCTTTTCTTATCTCAAAGCTGCTTCAGT
CTTTGTGCACAGGGGATGCTCAGAAGCGTGCCTTCTTTCAGGGAGACTGGCCATGCGCCTGAG
TTAGATGATAACATGGAGGTTCATCACACGCTGTCTACTTGAGTGTGTTTTTGGAATTCTCCA
TAATAAAAAGTTAAAAAATACAATTGATAGGTAAGAGTAATTGAAGTAGTTTCAAATTGGTTA
GCTATAAAATGCAACTATGAAGAGGATTGTAGGTAATTAAAATACTAAGATTGTATTGAGGAG
AAATATATTATTCAGAACAATACCTGTGACATGGCATTAGTGACAAATATGAC

FIGURE 45

TTCAGAGCCAGAAGGGCCTCGAGCTGCNAGCCCCNTGGAATGAAGCAGGCCTGGGCTGAGGCT
GGAAGGGAANCCCCTCTAAGCTGGNCCGGGGGCGGGAAAACTTACCACCAGGGGACTCGAGAT
GGGGAAGGAAAGGTCAGAAAGAGGAGNAGGCCCAGGCACGGGGTGTGGGCGGCCTGCAGAGCT
GGAGCCAGNTGCTCCGCCCAGAGCCAGGCATGCACACTCAGAGTAGGTGGCCTGTGCCACCGG
GGAAGAGGGGCGGGTCGGCGTGCTGCTGAAGATGCCAGGNAGCTGCCGGCCTGCTCTGTGCGT
GCTGAAAGGTGTGGTGAGAAGCACTTACAAAAAGAAATGGACTGTGTTAGGATTGCACATTTT
ACTTTGTTTCTCCCAAATACGTTCTCTTTGAATTTTTTTCCTTCCAGGGCCAGGACTGGAGTG
ATGGTTGAGACAGGCACGCACTGGGTCTTGTCTGCATTTACATTTTGAGATTTTGTTCAGCAT
GGATTTTATGGCGTTTTTTTGTTTGTTTGTTTGTTCGTTTTCAAAATACTGCACCGA

FIGURE 46

CCAGATTTNGTTTCTTTCTTTTTTNAAAAAAAGAAAAAAAAAXXXXXXXXXXXXXXXXXXX
XXXXXXXXXATCCTTGGGTGTGGGCTGATCACCTTGACCTCAGGTCTTTGTGCTATTGCCCTC
TCTGCTTTTGGGCACCTTGACCTCAGGTCTTTGTGCTATTGCCCTCTCTGCNTNCGGGCACCT
TGACCTCAGGTCTTTGTGCTGTTGCCCTCTCTGCTTTGGGCACCTTGACCTCAGGTCTTTGTG
CTGTTGCCCTCTCTGCTTTGGGCACCTTGACCTCAGGTCTTTGTGCTATTGCCCTTTCTGCTT
TGGGCACCTTGACCTCAGGTCTTTGTGCCGTTGCCCTCTNNGCTTTGGGCACCTTGACCTCAG
GTCTTTGTGCTGTTGCCCTCTGTGCTTTGGGCACTCTTCCTCAGACCTGTGCATCACATTCCC
TCTCTTCAGCTCTCTGCTCAAATGTCACCTCCTTCCTGACATCTTCCCTGACCATCCTAGCCA
AAATACC

FIGURE 47

CGCCCTAGCCCTCTGTGATTTCATAATGCTGGAAGTATGCTTTTTTAAAAAGTTTAAATTCTT
GCCCAATTTTACTGTAGCGGGAATAAATACATGCTAGTATTCTGAGAGTNTTATGAAACTAGA
CATAAAACAAGTTAAAATTAATGGGGAAATGGCTAGATGTCCATGACTGTCAGAGTCAGTACA
TTGTCAGTATCCTCCAGAAATGTCACTGATATTAAGCAAGCTGAGTTATTTCCGGCGTTGAAT
CCATGAAGAATGATAAATGTTTTCTCATCATACTTATTCTTAGAATGTTGTGATACTTTTGAT
ATTTCAGTTACTCGTCTTTAAAAGGGGAGTGCCCTTCCCTGGGCCTTGCCTAAGAGAAGAAAG
AAAGACTATATTAAGACAGAAAACATGGACATTTTAAAGAGACGAATACACTGCTATGTGAAA
TACCAGTTNTACTCAGTAAACTCCCTCGA

FIGURE 48

GCAGGCCCAAAGAAGAAGCTCAGGCTGAAATGAACCGTACCGCCTNCCGAGGGAGAAAGAATT
CNNGGCCAAGGAAGCTNCGGCATTGGGATCCCTTGGCAGTTGCAGCCACTGAAGTGGAGAAGG
AGACCCAGGAGAAGATGNCCTCCTCCAGACATACTTCCGGCAGAACGGGATGAAGTCTGGACA
ACCTCTTGGCTTTTGTCTGTGACATTCGGCCAGAATCCCTGAAAACTACCGCATAAATGGATA
GAAGAGAGAAGCACCTGTGCTGTGGAGTGGCATTTTAGATGCCCTCACGAATATGAGCTTAGC
ACAGCTCTAGTTACATCTTATGATATGGCATTAAATTATTTCCATATATTATATAATAGGTCC
TTCCACTTTTTGGAGAGTAGCAAATCTAGCTTTTTTGTACAGACTTAGAAATTATCTAAAGAT
TTCATCTTTTTACCTCATATTTCTTAGGAATTTAATGGTTATATGTTGTCTTTTTTTCCTATG
TCTTTTGGCTCAAGCAACATGTATATCAGTGTTGACCGA

FIGURE 49

CGGACGCTTGGGCNGCGCCAGCGGCCAGCGCTAGTCGGTCTGGTAAGTGCCTGATGCCGAGTT
CCGTCTCTCGGGTCTTTTCCTGGTCCCAGGCAAAGCGGAGCGGAGATCCTCAAACGGCCTAGT
GCTTCGCGCTTCCGGAGAAAATCAGCGGTCTAATTAATTCCTCTGGTTTGTTGAAGCAGTTAC
CAAGAATCTTCAACCCTTTCCCACAAAAGCTAATTGAGTACACGTTCCTGTTGAGTACACGTT
CCTGTTGATTTACAAAAGGTGCAGGTATGAGCAGGTCTGAAGACTAACATTTTGTGAAGTTGT
AAAACAGAAAACCTGTTAGAAATGTGGTGGTTTCAGCAAGGCCTCAGTTTCCTTCCTTCAGCC
CTTGTAATTTGGACATCTGCTGCTTTCATATTTTCATACATTACTGCAGTAACACTCCACCAT
ATAGACCCGGCTTTACCTTATATCAGTGACACTGGTACAGTANC

FIGURE 50

CATGGTGGTGCGCAACTGTAGTCCCAGGTACTTGAGAGGCTGAGGTGGGAGGATCATCTTAAC
CCCGGGGAGATGGAGGCTAAAATGAGCTGTGTTCACACCACTGTACCCCAGCCTGGGCAACAG
AATAAGACGCTGTTTCAAACAAAAATGTGTAACTCAAAAACAGCAAAATGCTTAGTTCTTTGT
AAATGCAACATTTTAGGCTACTGTTTATTTGCCAATAGAACTTTTTTTTCTCTCTCTCTCCTT
ATNTGTAAACTTAGCTATATATGTTTCTCACTCTTGGGTCTGTGTACTTCAAAATCTTTTAGA
AATXXXXXXXXXXXXXXXXAAAAAAAAAAATGGAATAATACAAAATTATACTAAGATTCATTC
ATGTTATTTTTTGTGGCTGCAGTGCATTCATTTCCACTATATAGTATTTCATTGTCTGATGTA
CCAGAATTTATCCACTCTCTTTTTGATGCATGTTTGGATTTGCAGTCTTTTGCTTTATGAAAA
GTGCTGCTGTAAAAATTATTA

FIGURE 51

TTTTTTTTTTTTTTTTTGGTTTGTTGTTGTAGTAGTCTGGTGCTGGCCACATTTAAGTCT
TAAAAATTTTTAAATTTTGTTGTTGATGTTTGTAGACAGCCCTGTTGTTGAAATCATGGCTTT
ATTCATTTTATTTATTTTCGAACC

FIGURE 52

TTTAATAGTTATTCGTCTTCTGTTGTATAGNCATTTAAGTTGNTTATATGTTTCTGTTATTAA
CCCTTTGTCCCACGTATGATTTGCAAATATTTTCTCCCATTTTTTTTCAGTTGTCTCATTTTG
TTGATTNTATCAGATTCCATGAAGCAGCTTTTTAANTTCAAGAAAAACGAATC

FIGURE 53

CGGAAGTCCCTTGAGGAGCGTCAGAAGCGGCTTCCCTACGTCCCAGAGCCCTATTACCCGGAA
TCTGGATGGGACCGCTCCGGGAGCTGTTTGGCAAAGATGAACAGCAGAGAATTTCAAAGGACC
TTGCTAATATCTGTAAGACGGCAGCTACAGCAGGCATCATTGGCTGGGTGTATGGGGGAATAC
CAGCTTTTATTCATGCTAAACAACAATACATTGAGCAGAGCCAGGCAGAAATTTATCATAACC
GGTTTGATGCTGTGCAATCTGCACATCGTGCTGCCACACGAGGCTTCATTCGTTCATGGCTGG
CGCCGAACC

FIGURE 54

CCCACTCAGATCTACTGAAACTGAAAACCTGGGAGCAGGGCCCAGCAATCAAGAGTTTTTAAC
AAACCCTCCTGGTCATTTTGATGCACACGCAAGTTTGAGAACCTGTGCCCTTTAGGAGGATTT
CCTTTTCCTCACTAAAAGCCCCCTGAAAGATGCCTCCAGGGTATGCCTCTGTGCCCTACTGCC
CACTGCTGCTTTCCTGTTTCCTAGGAATCCCCTTTATGAAGTACCCATCCTCCAGAAAGATTT
CTTACCTACCTTGAAAGGATCTTGGCTTCTCCACAAGGTTACTCCATCCTCTGAGCAGTTATT
TCCGATTCTACTTTTGAATGGTTTCTTTTCAGATCTTCCTCAGTGCTTTCTCTTTCTGGCTAC
CCCTCAAGCCCGA

FIGURE 55

ATATATATATAAATATAGAAATATATATATAGAAATATATATATATCTCTCTCCATATCCAAA
AGCAAGATTACAAATTTCAGTTGAGGGTAATAGCACTTAAAGTAGGAACAGAGATTCTTTATG
TGTTAGCATAATTCTTTTTTATTACAATTCTGTTACTAAAGAATCAGGTGTCATTAAAGGTGA
ACATGGTTACCTTCACCTTCTGCACAGCAGTTTTTCATATACTTGAAGACATTAAATCCCCTT
CCCCATCCAACTTAATCTTTTCCAGCGA

FIGURE 56

CGGACGCGTGGGCGGACGCGTGGGTGGCCTTAGAGTAGTTTTTTGAGCATTTATTGTGCTTGG
TGTTCTCTGAACTTCCTTAGATCTGTGGTTTGGTGTCTGACATTAATTTGGATAAATTTTCAG
TCATTGTTGTTTTAAATATTTCTTCTCTTCCTTTCTTCTCCTCTTGGTACTTTCATGTGTTTA
TATTACACCTTTTGTACCTGTCCCAGAGTTCTTGGGTATTATCTTCTGTTTTTTTTTGGGCCT
TTTTTTTTTCCCTTTGGTTTTCAGTTTGTATTGATACATCCTTAAGCTCAGAGATTATTCTTT
TTTTCAGCGGTGTCCACTCTCCTAATGAGCCCATCAGTGGCATTCTTCATTTCTGTCACCATG
CTTTGCTCTCTGGCACTTCTTTTCATTTTTTTCTTAGAATTCCTATCTCCCTGCTCATGCTGC
CCACCTGTTCCTGCAAGCTGCCTACTTTCTCCATTAGAGTCCTT

FIGURE 57

TGGTGTCTTTCCCACCACAGCCCNGAGAGTCAGTCATTTTTNCAAAGAAGCCNTGGTTGGCTT
TGTGGAGAATGATATATGTTATTATTATTNTCCGCAGCCAACATGACCGCTCCTCTGGTGTCT
TTCCCACCACAGCCCGAGAGTCAGTCATTTTTCAAAGAAGCCTGGTTGGCTTTGTGGAGAATG
ATATATGTTATTATTATTTTTTGTTTTGTTATGTTGTGTTTTTTAGACAGTCTCGCTCTTTGC
CCAGCCGA

FIGURE 58

GGAGTAAAAAGACTGTNAAACATTTTTTTTAAAAAATTATTTTTACATTACGACAATATATT
TANGGATGTGTTNAGATCAAAAATTAAANTTCTGTGTCCCAGATCTACTTTCAAAGTGAGATT
TTCACTTGTCAGCTTAAATTTNTGACTAGAACTAACATTTGTGTATTNTTGNGCTTAGTCGGA
ATACAAATTTCACAGTGGATTTTTGAAGTTTGTCCTTAAATTGGATAAAATCAAGTGATTAAA
GTTACTAAAGAGATAAAAATGGTAATTTCCATTTTTAAAAGTAATTTGGTTGTGTTTATAGTT
ATTTGTACAAGTATTTATCACAGCGAACC

FIGURE 59

AGCAATGCCCTGCCCCCAGTGGAGGATTAATTCCTATGNTGGGGACAACATTGTGACNGCCCA
GGCCATGTACGGGGGGCTGTGGATGTCCTGCGTGTCGCAGAGCACCGGGCAGATCCAGTGCAA
AGTNTTTGACTCCTTGCTGAATTTGAGCAGCACATTGCAAGCAACCCGTGCCTTGATGGTGGT
TGGCATCTTCCTGGGAGTGATAGCAATCTTTGTGGCCACCGTGGNAATGAAGTGTATGAAGTG
CTTGGAAGACGATGAGGTGCAGAAGATGAGGATGGCTGTCATTGGGGGCGCGATATTTCTTNT
TGCAGGTCTGGCTATTTTAGTTGCCACAGCATGGTATGGCAATAGAATNGTTCAAGAATTTTA
TGACCCTATGACCCCAGTCAATGCCAGGTACGAATTTGGTCAGGCTTTNTTCACTGGCTGGGC
TGCTGCTTNTTTCTGCCTTNTGGGAGGTGCCCTANTTTGCTGTTCCTGCGAACC

FIGURE 60

AACTTGTCAGAGGCAAGTGTCCAGAGTTTTGCTATANATTCATTATGGAAGGTTTNACCTTAT
TGAAATGACAGTTCCCCACCTTTAGCATTTTATATTGTTCCATTAACTGTCANACAAACATTC
CTGCAAAATATCAGTTCAGGAACCAAACTTACTTTCCCTGAGATGGTAACCGTTTCACAGCCT
NTCATATTGCTGCTTCATTANGTGATGAAGTCTAAACACGTAAATGGTGACCAGTTAAAACAC
ACACCTGCCGAACC

FIGURE 61

CCNANGGGTCCGGTTTTTTTGNATTTTTAGTAGAGACGGGGTTTCACCATGCAAGCCCAGCTG
GCCACGTAGGTTTTAAAGCAAGGGGCGTGAAGAAGGCACAGTGAGGTATGTGGCTGTTCTCGT
GGTAGTTCATTCGGCNTAAANAGACCTGGCATTAAATTTCAAGAAGGATTTGGCATATTNTTT
TCTTGACCNNNCTCTNTAAAGGGTAAAATATCAATGTTTAGAATGACAAAGATGAATTATTAC
AATAAATNTGATGTACACAGAGTGAAACATACACACATACACCNTAATCAAAANGTTGGGGNA
AAATGTATTTGGTTTTGTTCCTTTCATCCTGTCTGTGTTATGTGGGTGGAGATGGTTTTCATT
CTTTCATTACTGTTTTGTTTTATCCTTTGTATCTGAACGAACC

FIGURE 62

AGAGACGGGGTTTCACCATGCAAGCCCAGCTGGCNANGTAGGTTTTAAAGCAAGGGGCGTGAA
GAAGGCACAGTGAGGNATGTGGCTGTTNTCGTGGNAGTTCATTCGGCCTAAATAGACCTGGCA
TTAAATTTCAAGAAGGATTTGGCATTTTNTCTTCTNGACCCTTNTCTTTAAAGGGTAAAATAT
TAATGTTTAGAATGACAAAGATGAATTATTACAATAAATTTGATGTACACAGACTGAAACATA
CACACATACACCCTAATCAAAACGTTGGGGAAAAATGTATTTGGTTTTGTTCCTTTCATCCTG
TCTGTGTTATGTGGGTGGAGATGGTTTTCATTCTTTCATTACTGTTTTGTTTTATCCTTTGTA
TCTGAACGAACC

FIGURE 63

TCTTTAGAGATCTTTGACTTGACCNAAGGGTCCGCAAAGGGTTCGGGTTTTTTGTATTTTNAG
TAGAGAGGGGTTTNACNATGCAAGCCAAGNTGGCAAAGTAGGTTTTAAAGCAAGGGGCGTGAA
GAAGGAAACAGTGAGGAATGNGGCTGTTTTCGTGGTAGTTCATTCGGCNNAAATAGACCTGGC
ATTAAATTTCAAGAAGGATTTGGCATTTTTTTTTCTTGACCCTTNTCTTTAAAGGGTAAAATA
TTAATGTTTAGAATGACAAAGATGAATTATTACAATAAATTTGATGTACACAGACTGAAACAT
ACACACATACACCCTAATCAAAACGTTGGGGAAAAATGTATTTGGTTTTGTTCCTTTCATCCT
GTCTGTGTTATGTGGGTGGAGATGGTTTTCATTCTTTCATTACTGTTTTGTTTTATCCTTTGT
ATCTGAA

FIGURE 64

GTGTGTGTGTGTGTGTGTGTGTGTATGTGTATATATATATACATATATATACACATATGTATG
TATACCTAANTCCTAAAGTGGAACAGTAAGAGTCATTATTTATAGATTATNTGATTNTNTATG
TGGAAAGAGAAAAGAATCATATTAAGTACTTTGGACTGAACAATGACCCCCAAAATTNGTATG
ATGATGAAGCTCTCTNTAAATATTTTCTTGCTTTACTGGACTGATTTTAACCCGCT

FIGURE 65

AGGGATCCAGGTTGGTAGAGNAATCCCGGCCGGTTTCCCAGAGATGTTTAACCAGCACNTGCT
TNTGAGACTTCGTTTTNTGTTCCAGCAACCCTGGTTGGGGGGTCAGACTTGANACACTTTCAG
GTTGGGAGTGGACCCACCCCAGGGCCTGNTGAGGACAGAGCAGCCAGGCCGTCNTGGCTAANT
TTGCAGTTGGCANTGGGTTGGGGAGGAAGAGAGNTGATGAGTGTGGNTTCCCTGAGNTGGGGT
TTCCCTGCTTGTCCAGTTGTGAGCTGTCCTCGGTGTTACCGAGGCTGTGCCTAGAGAGTGGAG
ATTTTTGATGAAAGGTGTGCTCGCTNTCTGCGTTCTATCTTCTCTNTCCTCCTTGTTCCTGCA
AAC

FIGURE 66

ACTTAAAAATATTGTTGAGTTCTAAACNGATTTTTNGTATATATCATACATAGAAAATATTAA
ATTTTTGTTCTAAAACAACCAAAAATGGAGCATACATTTAGAGTGGCATTTGTTGCATATTAT
TAAACAAATGAAACTGANTNTTTTTTCATCCTGANGCAGATTANATCCCATTTTAATCTTTTT
CCTCTCTCCTTTTCTNAACCNACNTCAGAGTATCCTGTAACAGCTGTCCCTATAGTTTTCAAG
GAAAGTGATAATAATGAGATTACTTCTTCTTTCATCGTTTATTTTTTTGGGAGGATGGGGAAA
CCACAC

FIGURE 67

TCCCCTGAATATTCAGGAGGGAGAAGCAATCGCCCCAGGACAGAGACGGGGANATCCCAGGAG
CAGGGTACAGGNTTTAGCAATATCCATCTTGCGGTANTCCCTCCCTNACAACAACCAGAC

FIGURE 68

AAATGACCTATAAATAAGTTGGTTTGGGANATTATTATTTTTTTAGCATTATTTTTAAAATAG
ATNATGGTTNATATTTAATTGGAATTCCATAATNTAATGTACTGATAGGTAANTTGTGTGGAA
ATTGTTTNGCAGACATAAATTACTAAATAAATGTTCTGTTTTCAGATAGTTTAGTNTTTGNGA
CATTAAGTATTGGGACAGATTGTTTTGACTCCAATTAATATTCTGAAATTTTTCTCCTTTCAT
TACCTACCTNTCCATTATGCCTCAGTTGTAACGGTGAGTAAAACTATTTTTGTGTCTCATACT
TTCTTTATCTTTAAACTTTGTTTTACACAGTAATTATTTTCAACCATTNTTTGCTAACTGCAC
CTCGCTGCATGGTTCCTTCCTGTGTCCCACCAACCAGCCGCCACATTTTACCANATGTTCCCA
GTGTTCATGGGCCCTTTCCACCCTTGTCTCAAAATNTCCCTATTGATTTTATTTTGCTTTTGT
TANTCCCTTCAAACGCC

FIGURE 69

AGAGACGGGGTTTCACCATGCAAGCCCAGNTGGCCAAGTAGGTTTTAAAGCAAGGGGCGTGAA
GAAGGCACAGTGAGGTATGTGGCTGTTCTCGTGGTAGTTCATTCGGCCTAAATAGACCTGGCA
TTAAATTTCAAGAAGGATTTGGCATTTTNTTTTCTTGACCCTTNTCTTTAAAGGGTAAAATAT
TAATGTTTAGAATGACAAAGATGAATTATTACAATAAATTTGATGTACACAGACTGAAACACA
CACACATACACCCTAATCAAAACGTTGGGGAAAAATGTATTTGGTTTTGTTCCTTTCATCCTG
TCTGTGTTATGTGGGTGGAGATGGTTTTCATTCTTTCATTACTGTTTTGTTTTATCCTTTGTA
TCTG

FIGURE 70

ACACCAATGCAGTGAGGTCGGGGATTCCCCAANTGGATCCATNGCACCAGGTTCAAGNTAACC
CCCAAGGCAGTTTTTTCTTCCAAAACATTAACAGNTAAGTGTTTGTNTGGGCCAATTTNTCNT
ACCAAGTTTAAATTAACCAACATTTTTTTTTAAAACCAAAACACAAGGAAGACTAACCACGT
GNTTCCAGGAATGGCCTGTATTTACCCAACCACTTTNTATACNTNTTTTCCAACCAAAAGTNT
TAATATGGGAATATCCCTCACCACGATCCTAATACTGTCAGTAGCTGTCCTGCTGTCCACAGC
AGCCCNTCCGAGCTGCCGTGAGTGTTATCAGTTTTTGCACTACAGAGGGGAGATGCAACAATA
CTTTACTTACCATACTCATATAGAAAG

FIGURE 71

GTTCAGGACCAAGCGGTAAGAAGGCNTGAGGACCCAGGCCCCANTGGAGCAGTNTGTCCTTAT
GCCGAATCAAGGCGGAACATGGGTGAAAGACGAGTAAGGGGCAAATCACAGAATATTCCACAG
CGCCCTCCAGAGTTACNTGGGGAGGACCGAGGCCACACGCCACTGCCCCCGAGGCCAGAGTGT
AAGTAAAGGATAACCAGGACTCGCTGGGAGAGATGGATTCTGTCCTCAGCAACANTCCACAGC
AGAAAGGGGTAGCAGGTACCCCTTTTTATCAGCGGTAAAAATGCATTTACAACCTTTCATTTA
ACCGAAAAACACAGACCGCTTTAACCTTTTTATTTNTGTCCCCCACTGCATGAACATTTATAC
AATTTTAAAAATACTTCCTCATAGGATGCTTTGGCCCTTCATCTATTTAATCATAGCTACATA
CCTATTTTTTATAAGTAGCAGTACACATTCAAAGGGGTATTCCTAGCTCAATGCTTGGTGTTN
TAGTTCAACTTTTATCCTGCAG

FIGURE 72

TAGAAATAACCCTTTTCCTTATTNGATTTTAGTCATCAAACATAGTATGATATGGGAAAAGTC
AGCCATTTACCAGAAATTATCTTATTTTGATTTTAAAAACTCATTTCTATATGTAGTTATTGT
AATGTCTATTTTTTTAGACTTAAAGATTTATAGAAGACTATAGTTATCTGATTTGTTATTTGG
CATTTTTTCATTCTGTAAATCTTTGCTTATGGCACATTGTGCTCTCTGTTTTCCATGGTTTTA
TTCATTTATCTCCTCCTATTTNGAGGGGACAACATGGGTAGTTAAATCTTTGTCAATAGTATT
GGAGATAACACTAACTGCTATTATCATAACATNTTCATTTTTACTGCATGC

FIGURE 73

GGACTGAATNCACTTGTAATGGTGACCACTGAAAGCTGCAGAGGGACAGTAGGTATTTNATNA
AATGCCTTATATGGCATTCTATATGAAGAACCTCTGAACCCAAAGTATATTATTTAGAAAGAA
AGATAAAGAGATATAAGCAAAGTAAGAATATATCTTAAAAGTATCTTATAAACCATTAACTTA
TAGTGGTAAGATAAACCCTCTATCAGCAGGAAAATACCTGCATATGCATACATAAGGAAGACT
GTGCACCTAATCTAGGGATACATAATAAGGTGGACTCTGTATTAGTAGTAAGTATTTTTATAA
AATAATACTTAGAACAAATTATATAAGATAATTATAAATATTAAGATCTTTATATTGCATTGC
TTCTGACTTAAAAAATGAATAAATAAATGGGGTCTTGCTATGTTACCCAGGCTGGAATGCAGT
GGCTATTTACAGGCACAATCATAGTGCACTACAGCCCCAAACTCCTGGGCTCGAGCAATCCTG
TTGCCCAGCCTCCCAGGTAGCTGGGACTATATATAAGCAGGCACCACTGTGCCTGGCTGCTTC
TGACTAATCCAAGTAAGAATAATAAATCTATGACAAAGTTATACACAATCTCCTACCCCTACC
TCAG

FIGURE 74

ATGGAACCCAGTTGGAAACCACTCTTCACGNTTATTTATCCNGGGGAACTTCCCCCAACNTAG
CCAAGGCTTCGGTTGAGTTCTCACTCCAAAGGTGGGAACTGGACCATGGGNACACTTGGACAC
GGATGGGGAACTCACACACCGGGCCTGTCTTGGGGTGGCGGTAGGGCGTAGCGATAGCATAGG
AGATACACCTAATGTAATGACGAGTTATGGGTGCAGCACACCAAATGGCACTGTATACGTATG
TAACAAACCTGCACTTGTGCACATGTACTCTAGAACTTAAAGTATAATATAAAAATTTTAAAA
ATTTTAAAAAAATAAAAAAATCACTGGGCTAAAGTAAATAAGTATTTTACTGGTTCTAAGATT
GTTTTTCAGAGAGAAAAACAATAGAAGTGTAGAAGCAATTCGATAAAGAAAGGAGTCTTTTCA
ACAAATGTTGCTGCAACAGTCAAATGTCTGTATGCAAAAAAATGAACCTCCA

FIGURE 75

TGGAAAAAAAAAAAAAAAGCCCCTTTTCAGTTTGTGCCACTGTGTATGGTCCGTGTAGATTGA
TGCAGATTTTCTGAAATGAAATGTTTGTTTAGACGAGATCATACCGGTAAAGCAGGAATGACA
AAGCTTGCTTTTCTGGTATGTTCTAGGTGTATTGTGACTTTTACTGTTATATTAATTGCCAAT
ATAAGTAAATATAGATTATATATGTATAGTGTTTCACAAAGCTTAGACCTTTACCTTCCAGCC
ACC

FIGURE 76

TTTAGGGTTCCTTGACTTGNACCAAGGTTTCGGGGAAATTTAAAGGNTTAAGGAANGGGAGGA
AANGTTTCTTAAATTTGGAATTAACAGTAATAATTTTTGGAAATTCCAATAAAATTGGCAAAA
GATTGGGAAATTTTGGANGAATAAGGGAAACAGATANTTTTCNGGGTATTCAGGTAAAGTTTA
AAAAAGGTTTTAAAAGAGAGTTTTTCTAACATTTTGAAAAGCAACATGAAAAATGAAAACAGT
TTTAACAGATATACAATATGGATGACTTATATACAAATGACNTTAAAATATATTAAATTCATT
ATAGTAGTTATATTTAAGTAAAATATGATGAAATTTAATAGAGATTCACTCNTCCCAAAAGCA
CCTTCATGGAAGATTCNTCATTAACAGGCAGTCCTTTAGTATGCTGATTTATACAAAATGCTG
AAAAGAAGAGAAATACCCCAAGTTCTTGAAAAAAAAATTTTTTGATATGACTACTCTAACAGTA
ATAACTATAAATCTCACTTTAAATAATTTAAAACAAATTAAAGTGATATATGAGTTAAATGAC
CAAGCAGACTTGATTNTAGGAATGTTAAGGAATGTTCATTATTTGTTTTGGATAATGAAG

FIGURE 77

TTTGAAAAGTTTAAAAGGGAGGAAGTGGTTTTTATGATTTGGCCGTTTCCGGTTGCCNTNCAG
AGAGTTCCTTGCCTTCCCTGCCCTTGAAGGTGACNTGTGGCCCNTTTGGGTGNTGATGGACCT
GTGTTCCCACCCTGGTTCAAAAAGCAAAGAAAAGGGAGTGGTATCAGAAAATGGAAGAAGAGA
GTAAAGAAGACAGTGCTGGCTTGAGAGAAGCAGTGGCTTCAGGTAAAAGGNTACTGCCAGCGA
TATGGACGGGAGACAGAGAAATGNTAGAAGAGGGCGGTTCCCCAACAAAGGCCCCACCCACAA
GCCTGGACACCTGTGGCCCTAAATGAGAACAGGCATTCCTGTTTTTGCACCCAAAAAGTGGTT
TTTTGGTATGCCACACCCCCTATCCTATACCCATATAAACCCTGAACCCCAGGNTCCAGCTCA
GACCAGCAGAGGAGGAGACGAGACAAGCAGACAATGCAGAACAGTGCAGCAGAGAGAANTNGA
GAG

FIGURE 78

CCACGGTGTCCGTTCTTCGCCCGGCGGCAGCTGTCCCCGAGGCGGGAGGAGCCCGAGGGGCGC
GAGCCCCGCATGAATCATTGTAGTCAATCATTTTCCAGTTCTCAGCCGTTCAGTTGTGATCAA
GGGACACGTGGTTTCCGAACTGCCAGCTCAGAATAGGAAAATAACTTGGGATTTTATATTGGA
AGACATGGATCTTGCTGCCAACGAGATCAGCATTTATGACAAACTTTCAGAGACTGTTGATTT
GGTGAGACAGACCGGCCATCAGTGTGGCATGTCAGAGAAGGCAATTGAAAAATTTATCAGACA
GCTGCTGGAAAAGAATGAACCTCAGAGACCCCCCCCGCAGTATCCTCTCCTTATAGTTGTGTA
TAAGGTTCTCGCAACCTTGGGATTAATCTTGCTCACTGCCTACTTTGTGATTCAACCTTTCAG
CCCATTAGCACCTGAGCCAGTGCTTTGTGGAGCTCAC

FIGURE 79

GTTTGTCCCTTTTTCCNGTTTTTTTTGGACAAATTCAGTATACCAAGCAACATNAATTCCAGT
TTNGGTGGATTCCCGGGGTCTTTTGGGATCCTTGACTTGACCAAGGGTCNGGCCCTTTTCNGT
TGGGACGTTTGTAAGTTTTGGGCAGTTTCCGGGNGANTNGGGANTCGGGTTTNGCTTTCTGTG
TTCCATTCGCCCGGNGCGGTGGTGCAGGTTTTCGGGCTAGTCATGGGTCCCCGTTTCGGAGAC
TGCAGANTAAACCAGTCATTACTTGTTTCAAGAGCGTTCTGCTAATNTACACTTTTATTTTCT
GGATCACTGGCGTTATCCTTCTTGCAGTTGGCATTTGGGGCAAGGTGAGCCTGGAGAATTACT
TTTNTNTTTTAAATGAGAAGGCCACCAATGTCCCCTTCGTGCTCATTGCTACTGGTACCGTCA
TTATTCTTTTGGGCACCTTTGGTTGTTTTGCTACCTGCCGAGCTTNTGCATGGATGCTAAAAC
TGTATGCAATGTTTCTGACTCTCGTTTTTTTGGTCGAACTGGTCGCTGCCATCGTAGGATTTG
TTTTCAGACATGAGATTAAGAACAGCTTTAAGAATAATTATGAGAAGGCTTTGAAGCAGTATA
ACTNTAC

FIGURE 80

GGCGGTATCTTTTTTGCNAGTTGCAATTGGGGGCAAAGGTGNCCCTGGAGAATAATTTTTTTT
TTTAAAATGAGAAGGCCACCAAGTCCCCTTGGTGATCATTGNTACTGGTACCGTCATTATTTT
TTTGGGCACCTTTGGTTGTTTTGCTACCTGCCGAGTTTTTGCATGGATGCTAAAACTGTATGC
AATGTTTCNGACTCTNGTTTTTTTGGTCGAAATGGTCGCTGCCATCGTAGGATTTGTTTTCAG
ACATGAGATTAAGNACAGCTTTAAGAATAATTATGAGAAGGC

FIGURE 81

GTATGGCAGAGGATAAGGCGTTATGAGAAGCTGCCAAGCTTCAGATGTGCAGNTGGGNTGAAT
ACCGACGCCAGCGCNTAGCGCCCATTACTTTGCACCCACACTTAGGAAACAACCCACGCCTCA
CCGCGGGACCCGGACCCAGCCNTCCAGCACCCAGCNTCCGGTTCCGACGTCCGCGCGTGACCT
CCGGGTACCGGAGGACCTTGGGACGAGGAGGTCCCTCCGCTTTCCGGTAGGATATATCTGCAT
NTTGAAAGGAAGATAAAACAAAAGCCTTNTTTGGAATAGATGGATTTTTGTCACTTTCTGTGT
GAACTAAAGTGATTCAATGTNTCTTTTGGATTGCTTCTGCACTTCAAGAACACAAGTTGAATC
ACTCAGACCTGAAAAACAGTNTGAAACCAGTATCCATCAATACTTGGTTGATGAGCCA

FIGURE 82

ACTGATCAAAGGCAGGCGATACTTCCTGTTGCCGGGACGCTATATATAACGTGATGAGCGCAC
GGGCTGCGGAGACGCACCGGAGCGCTCGCCCAGCCGCCGCCTCCAAGCCCCTGAGGTTTCCGG
GGACCACAATGAACAAGTTGCTGTGCTGCGCGCTCGTGTTTCTGGACATCTCCATTAAGTGGA
CCACCCAGGAAACGTTTCCTCCAAAGTACCTTCATTATGACGAAGAACCTCTCATCAGCTGTT
GTGTGACAAATGTCCTCCTGGTACCTACCTAAAACAACACTGTACAGCAAAGTGGAAGACCGT
GTGCGCCCCTTGCCCTGACCACTACTACACAGACAGCTGGCACACCAGTGACGAGTGTCTATA
CTGCAGCCCCGTGTGCAAGGAGCTGCAGTACGTCAAGCAGGAGTGCAATCGCACCCACAACCG
CGTGTGCGAATGCAAGGAAGGGCGCTACCTTGAGATAGAGTTCTGCTTGAAACATAGGAGCTG
CCCTCCTGGATTTGGAGTGGTGCAAGCTGGAACCCCAGAGCGAAATACAGTTTGCAAAAGATG
TCCAGATGGGTTCTTCTCAAATGAGACGTCATCTAAAGCACCCTGTAGAAAACACACAAATTG
CAGTGTCTTTGGTCTCCTGCTAACTCAGAAAGGAAATGCA

FIGURE 83

AGGCTTTCATTCCCCACCTANGGAGTTAATTTTTTGGATTAAAAGGTTTTTAGAACTTTTTGT
TGATGGTTGGTTTTATTAAGGCCCGGAAGAAACATTCAGATTCGATTGAGGACCAGGAAATGG
CCTTNTAGGGAAGAGAAGGCATTNTGCTAGATGGCTTTTAAAAATATTTCCGCCAGAGTCACT
TGTCTCATTAACAACAGTTTTTGTCTTAGAAGTCTNTCTGTGATTTTATAAACTAGCATGATT
TTGTTATGAATGCATGCTGCTCTGGTTCTCTAATAAGCCCAACATGCATTTGCATCATGTCGG
CAATAAGCACTTTTTTTGCTGTGTTAACAATGTCATNTTCATTGTTGTGTGCCTGTGTTTTGA
CTGTGACCTGTCACATGAGGTTGGGTGTGGAATTTTCCACTTGTGGCAA

FIGURE 84

TCTTTGGAGCTGCAGGAGGGACGGATGGCGGAACCTTCCAGTCCCCTTCAGAGGCGACTGCCA
CTCGCCCGGCCGTGCCTGGACTCCCTACAGTGGTCCCTACTCTCGTGACTCCCTCGGCCCCTG
GGAATAGGACTGTGGACCTCTTCCCAGTCTTACCGATCTGTGTCTGTGACTNGACTCCTGGAG
CCTGCGATATAAATTGCTGCTGCGACAGGGACTGCTATCTTCTCCATCCGAGGACAGTTTTCT
CCTTCTGCCTTCCAGGCAGCGTAAGGTCTTCAAGCTGGGTTTGTGTAGACAACTCTGTTATCT
TCAGGAGTAATTCCCCGTTTCCTTCAAGAGTTTTCATGGATTCTAATGGAATCAGG

FIGURE 85

CAGGAACCTCTTTAAGAAAGTNTATTGTTACTNAAAACACACCACTGTCTTCTGGATGCTTTT
CTGGTTGCCTTTGAAGTTCATGCAGGTGGAGGACGTGGACATTGACGAAGTTCAGTGTATTCT
GGCTAACTTGATATACATGGGACACGTCAAAGGCTACATCNCGCATCAGCATCAGAAGCTGGT
GGTCAGCAAGCAGAACCCATTTCCTCCCCTGTCCACGGTGTGTTGAAAGTACACGGAGCCCCG
AGGACGGGTGAGCAGTTGTTTCTTTCCACTTTGGTTGTGCTGATGAGACCGGTCCGGTACTGC
AACAAGGCG

FIGURE 86

CAACATTCTGGACCACTAANCCTCTCTTGGCAACACTNGTTGGACAGATCCTGAAGATATGGG
NGACCTATTCCTAGAATGTTGCTGAAGCTTTTCTGGATGGTGGTGAATATAATTCTGCACTTC
CCCTCCTCAGTGCTCTTGTTTGCTCTGAAAGATACAACCTTGCAGTAGTTTGGCTTCGTCATG
CAGAATGTTTAAAGGCCTTAGGCTATATGGAGCGAGCTGCTGAAAGCTATGGCAAGGTGGTTG
ATCTGGCCCCACTCCATTTGGATGCAAGGATTTCACTTTCTACCCTTCAGCAGCAGCTGGGCC
AGCCTGAGAAAGCTCTGGAAGCTCTGGAACCAATGTATGATCNAGATACTTTAGCACAGGATG
CAAATGCTGCACAGCAGGAACTGAAGTTATTGCTTCATCGTTCTACTCTGTTGTTTTCACAAG
GCAAAATGTATGGTTATGTGGATACCTTACTTACTATGTTAGCCATGCTTTTAAAGGTAGCAA
TGAATCGAGC

FIGURE 87

AAATGTATGTATCATCAGTTGGNTACGTTTTGGTTCTATGCTAAACTGTGAAAAATCAGATGA
ATTGATAAAAGAGTTCCCTGC

FIGURE 88

CGGGTAACTTAGTGTTTTTGCNACAAGGGAAATTTTTTTTTCAGCCAGGGGGNGGGGGCCCTG
TGGNATCATAAAAAGGTCCTGGCATGGNTAACAGCCATTTTGGCCANTTTGCCGGAATTTGTG
GTTTATAAACTTCAGATGGAAGACCAGAAATAACAAGTGTGCATTTAGCAGAATTCCCTTCCT
GCCAGNTGATGAGACATTNTGGAAGCATTTTCTGACTTTAAAAATGAACATTTCGGTTCTTGT
CCTCCCCCTATTTATTTTTACATTTCTCTATGTGCAAATGAGAAAAACACTAAGGTTCAGGGA
GCAGAGGTATAGCCTTTTCAAGCTTGTTTTTGCCATAATGGTAGTCTTCCTTCTGATGTGGGC
GCCCTACAATATTGCATTTTTCCTGTCCACTTTCAAAGAACACTTNTCCCTGAGTGACTGCAA
GAGCAGCTACAATTTGGACAAAAGTGTTCACATCACTAAACTNATNGCCACCACCCACTGCTG
CATCAACCCTCTCCTGTATGCGTTTCTTGATGGGACATTTAGCAAATACCTCTGCCGCTGTTT
CCATNTGCGTAGTAACACCCC

FIGURE 89

CAGGAATCTCGAACACTGGCTCCTCCCCTTAGTTCCCGCCCTCGGAGTCAGCAAGCAGGGGGA
GTNTGAGGNCCCTGGGACAGCTCTGACTCTGGCTGACACACCTGCCTCTGGGCAAGGGTGGTG
CATATCTGAGGCGGACAGGCACACATGGAGAAGTCAGAGTCCACGCCCTCTGCTCCATCCCAG
TAGCCACCGTCTCAACTCAGCCCCTCGTCACTTCACACTTTGGCAGTGGTTTCTGTCCACTCA
GCTGGTTCAGTTGGCTCTATCACATCTCCCGGCCTCTAGGGTTGGCTCAGGCCCACCTCCGTC
CTCTCATAGGGCTGGCCATCCAACCATATCACTCCTCTCACGGCTTTTAAGGATAAAGTTTGA
AGCCTTAAGGATACGTCACAGGTCCTCTAGGCCCTGCTTACCTCAGCTTCTGCCTAGAAGTTT
ATGCCCCAGAAACAGTGAAACCTCCATGTTTACCCTCACACAACCTGTGTGTCTCAACACCAT
ACTTTTGCTCATACTGG

FIGURE 90

TCCGGGCCCCCGGGGACGCTGTCCCTGAACTTGCCGGGGAGCNGCCCCCGGCGTCCCGCGCGT
CCCCGCGTCCCTGGCAATTCCCGACTTCCCAACGGGCTCCCTGCTGGCAGCCCCCGNAGCCGC
ACCATGTTCCGCCTCTGGTTGCTGCTGGCCGGGCTCTGCGGCCTCCTGGCGTCAAGACCCGGT
TTTCAAAATTCACTTCTACAGATCGTAATTCCAGAGAAAATCCAAACAATACAAATGACAGTT
CAGAAATAGAATATGAACAAATATCCTATATTATTCCAATAGATGAGAAACTGTACACTGTGC
CACCTTAAACAAAGATATTTTTTAGCAGATAATTTTATGATCTATTTGTACAATCCAAGGATC
TATGAATACTTATTCTTCAGATATTCAGACTCAATGCTACTATCAAGGAAATATTGAAGGATA
TCCAGATTCCATGGTCACACTCAGCACGTGCTCTGGACTAAGAGGAATACTGCAATTTGAAAA
TGTTTCTTATGGAATTGAGCCTCTGGAATCTGCAGTTGAATTTCAGCATGTTCTTTACAAATT
AAAGAATGAAGACAATGATATTGCAATTTTTATTGACAGAAGCCTG

FIGURE 91

TTGAGCTCGATATCCCACAGAGCNTCCAGCAGAACGGTTCCCTTNTACATCCCACGTTTACTT
CACCNAAGAGTGGCTTCCCACCCAGACCCCCGGCAAAAGCCCTNTACCCNCCGGNTTGCCACA
GTCCACATGTCCCGGATGATCAACAATACAAGCGCAGACGATTTCAGAAAACCAAGAAACTGC
TGACAGGAGAGACAGAAGCGGACCCAGAATGATCAAGAGGGCTGAGGACTATGGGCCTGTGGA
GGTGATCTCCCATTGGCACCCCAACATCACCATCAACATCGTGGACGACCACACGCCGTGGGT
GAAGGGCAGTGTGCCCCCTCCCCTGGATCAATATGTGAAGTTCGACGCCGTGAGCGGTGACTA
CTATCCCATCATCTACTTCAATGACTNNTGGAACCTGCAGNAGGACTAGGGCCCCATCAACGA
GAGC

FIGURE 92

CCCTGCTGTCTTGGGGCCCTGGTTTGGTGCCCTTTGCCAAAANAGCGGTAGGTCCCCTGGACN
GAACCAAAATNATCTTCCCAAGTGTCTTCAAAAAGATTTTCTGCCAAGGNGGCCTTCCGGGTC
GTATACTACACNTACCTGCGANGAGGGATTTNTCAGCTTGTGGGGCGGGAANTCGGCCACCAT
GGTGTGCGTGGTGCCCTANGCCGCCATCCAGTTCAGCGCACACGAGGAGTACAAGCGCATCCN
GGGCAGNTANTATGGCTTCGGTGGAGAAGCCCTGCCCCCTTGGCCTTGCNTTTTCGCCGGCGC
ANTGGCTGGAACGACAGCCGGTTCACTGACNTACCCCCTGGACCTGGTCAGAGNGNGGATGGC
NGTAACCCCGAAGGAAATGT

FIGURE 93

AACTTAATGCAAAGGGTGTGAGATGTTCCCCCCNGCTGTAAAATGAAGGNCTATTGNTATTTA
TTGAGCTTTGTGGGANTGGTGGAAGCAGGCCCCCATGGACCATGCCCCCNCCCT

FIGURE 94

GGCAGCCGCGGCATGTCTATAGCAACTTTTTTANTACCANCCAAGTTTGTAGAACATTATCCA
ATATGTGGACTNTCACAATCATTGGGATTGGACCGGATAAGTTAATAAATTTGGCCTTATTTG
NTTGGAAGTGATTATACCGAAGGAATNCCAACTGTGGGTTGTGTAACCGNCCATGGNAATTCT
ACAATGAATTCCCTGGGCATGGCCCTGGAACNTCTCCTAAAATTCTCAGAATGGTGGCATGAA
GCTCAAAAAAATCAC

FIGURE 95

GGGTTTTTTTTTTTTGGTCTGGCCTCTTTCATTTAGCTTAATGTTTTCAAGGTTCATCTATGT
TGTATCACGTATCAGTACTTTATTTTTTGTGTGGCACGTCATATGGATACCCCACAACCCGTT
TATCTTTTCATTAATTATGGGCG

FIGURE 96

TTTTTTTTTTTTTTTTTTTTTTTTGAGACGGAGTNTCATTCTGTCGCTCGGGCTGGAGTGCAG
TGGCGCCATCTTGGCTCACTGCAACCTCTGCCGCCAGGTTCAAGTGATTCTCTTGCCTCAGCC
TCCAGAGTAGCCGGG

FIGURE 97

GTTTTTGTTACAGTTTTTGCCCACCATGGTTGCAGTTATAATGATGAGCTGCAGTTTTTGGAG
AAGATTCAATAAAAANTGNTGGAGGATCAAGAAGGGTTTGTGCCCAACATGCAGGTTGAAGGT
GTTTTNTATGTGAATGATGNTTTGGAGAAATTGATGTTTGAGGAATTAAGGAATGCCTGTNGA
GGTGGTGGTGTTGGTGGTTCCTGCCAGCCATGAAACAGATTGGCAATGTGGCAGCCCTGCCTG
GAATTGTTCATCGATTTATTGGGCTTCCTGATGTCCATTCAGGATATGGGTTTGCTATTGGGA
ANATGGCAGCCTTTGATATGAATGACCCTGAAGCAGTAGTATCCCCAGGTGGTGTNGGGTTTG
ANATNAANTGTGGTGTCCGCTTGCTAAGAACCAATTTAGATGAAAGTGATGTCCAGCCTGTGA
AGGAGCAAATTGCCCAAGCTATGTTTGACCANATTCCTGTTGGGGTGGGGTCAAAAGGTGTNA
TCCCAATGAATGCCAAAGAATTGGAGGAGGCCTTGGAGATGGGGGTGGANTGGTCCTTAAGAG
AAGGGTATGCCTGGGCTGAAGACAAGGAGCC

FIGURE 98

AATTAGAAAAGGAAGGTTTATTTTTAANATTCTTCTTCCAATTGGTTTAATGGTGAATTAATG
AAGNGGGTAAGCAAAACCAGGTGCTTGCGTTGAGGGTTTTGCAGTGGNTGGGAGGACCCCGGG
GTTTCCCCGTGTCTTTTCCANGAATNGTTCGGCCCCTTTGGAATAAAANACCCGCGAGCCCCG
AGGGCCCAGAGGAGGCCGAAGTGCCCGAGNTNCTNCGGGGGTCCCGCCCGCGAGNTTTTTTTT
TGCCTTNGCATTTCCTCCTNGGGCGTTTTGGANATGCCAGGAATAAAAAGGATANTNACTGTT
ACCATTTTGGNTTTTTGTTTTCCAAGCCCTGGGAATGCACAGGCACAGTGCANGAATGGCTTT
GACCTGGATTGCCAGTNAGGACAGTGTTTAGATATTGATGAATGCCGAACCATCCCCGAGGCC
TGCCGAGGAGAAATGATGTGTGTTAACCAAAATGGNGGGTATTTATGCATTCCCCGGACAAAC
CCTGTGTATTGAGG

FIGURE 99

ATACCAAGCAGGCCTTTGGCATCATGAACGAGCTGCGGNTCAGCCAGCAGCTGTGTGANGTCA
CACTGCAGGTCAAGTACCAGGATGCACCGGCCGCCCAGTTNATGGCCCACAAGGTGGTGCTGG
CCTNATCCAGCCCTGTTTTNAAGGCCATGTTCACCAACGGGCTGCGGGAGCAGGGCATGGAGG
TGGTGTCCATTGAGGGTATNCACCCCAAGGTNATGGAGCGCCTNATTGAATTTGCCTANACGG
CCTCCATTTCCATGGGNGAGAAGTGTGTCCTNCANGTNATGAACGGTGCTGTNATGTACCAGA
TTGACAGCGTTGTCCGTGCCTGCAGTGAATTCCTGGTGCAGCAGNTGGACCCCAGCAATGCCA
TNGGCATNGCCAAATTTGCTGAGCAGATTGGCTGTGTGGAGTTGCACCAGCGTGCCCGGGA

FIGURE 100

TTGGCATATTTTTTCCCAGCTTAATTCAATTCCAGCATTGTCATGCAGCACGGNAATCCTTTG
ATTCCACAGANACATATCCCCAGCATGCGCAGTTTTTGGATGGCACCACCAGCAGNTTTATCC
CCCTGTACCGATCCTCAGAGGAAGAGAAGAGAGTGACAGTTATNAAAGCCCCGCATTACCCAG
GGATNGGGCCCGTGGATGAATCCGGNATCCCCACAGCAATTAGAACGACAGTTGACCGGCCCA
AGGANTGGTACAAGACGATGTTTAAGCAAATTNACATGGTGCACAAGCCGGATGATGACACAG
ANATGTATAATANTCCTTATACATACAATGCAGGTTTGTACAACCCACCCTACAGTGNTCAGT
CACACCCTGCTGCAAAG

FIGURE 101

CCAATCGCCCGGGGCGGTGGTGCAGGTNTCGGNTAGTCATGGGGTCCCCGTTTCGGAGACTGC
AGACTAAACCAGTCATTANTTGTTTCAAGAGCGTTTTGCTAATTTACANTTTTATTTTTTGGA
TCACTGGCGTTATCCTTNTTGCAGTTGGCATTTGGGGCAAGGTGAGCCTGGAGAATTANTTTT
NTTTTTTAAATGAGNAGGCCACCAANGTCCCCTTTGTGCTCATTGNTANTGGTACCGTCATTA
TTTTTTTGGGCACCTTTGGTTGTTTTGCTACCTGCCGAGNTTTTGCATGGATGCTAAAACTGT
ATGCAATGTTT

FIGURE 102

TGTTCCCTGGTGGCAGCGAGGTGGGCGGCGGCGGAGGGAGNTGGACCCCATGGAAGTCCGCGG
GTGAGTGAGACCCGGCGCCCACGGTCAATCCCCGCAAATTTCCTGGGCCCTCCCCGACGGCCT
NCCTGCCCTTTTGTTTTAANTTTTTATTAAAATGCTTAGGATACAGATTGANTTTTTTTTGTA
AATGACTGTTTTANTTTTCCTGAAGTAGGANATATATGCACTTTGATAAAACAGAATGAGAAG
TNATAATTCATGGGNATTCNTATACAAGGTGCTGATCCTGTGTTTGGAGCTGAGCTCCTCACA
GCAGNTTTTTTCAGCTATTTT

FIGURE 103

TGCCGCGTTCATTTTTTTNGCCATTTGGCACATTATAGCATTTGATGAGCTGAAGACTGATTA
CAAGAATCCTATAGACCAGTGTAATACCCTGAATCCCCTTGTANTCCCAGAGTACCTTATCCA
CGCTTTTTTTCTGTGTCANGTTTNTTTGTGCAGCAGAGTGGNTTACANTGGGTTTCAANATGC
CCCTTTTGGCATATCATATTTGGAGGTATATGAGTAGACCAGTGATGGANGCCCCAGGAATTT
ANGACCCTACAACCATTATGAATGCAGATATTNTAGCATATTNTCAGAAGGAAGGATGGTGCA
AAATAGCTTTTTATTTTTTAGCATTTTTTTACTACCTATA

FIGURE 104

CGGTGGGAATTTAGTTTTTCCAGGATGTGGTTGCCCCTTCCGNTGTGGGGGGAAAGGGGCCCC
CAGAACCGACCANACCGTGGCAAGAGACCCAGAACCCGAGGACGAAAAATTGTATGAGAAGAA
CCCAGATTCCCATGGTTATGACAAGGACCCCGTTTTGGANGTTTGGAACATGCGAATTGTNTT
CTTTCTTTGGCGTNTCCATNATCCTGGTCCTTGGCAGCACCTTTGTGGCCTATTTGCCTGANT
ACAGGATGAAAGAGTGGTCCCGCCGCGAAGCTGAGAGGNTTGTGAAATACCGAGAGGCCAATG
GCCTTCCCATNATGGAATCCAANTGNTTTGACCCCAGCAAGATCCAGCTGCCAGAGGATGAGT
GACCAGTTGNTAAGTGGGGNTCAAGAAGCACCGCCTTCCCCACCCCCTGCCTGCCATTTTGAC
CTTTTTTCAGAG

FIGURE 105

AACTTCGGTGAGGGTGCCGTTANCTGCTGTTCCTGCAGNGATTATGGGGATTTTTTCGGGGG
TTTGTGCGNTANGAATTTGAGGCCGACGCCCATTGGTGTTCAGAGAGACGCAACAAGAANTTG
AGGACATGGAGAACGAATTTTACTATNGCTACCCAAGNTTCCAGGAAGTGCAAGTGATGGTTT
TNGTGGGCTTCGGCTTCCTCATGACTTTCCTGCAGCGNTACGGNTTTAGCGCCGTGGGCTTNA
ANTTCCTGTTGGCAGCCTTCGGCATCCAGTGGGCGCTGCTCATGCAGGGCTGGTTCCACTTNT
TACAAGACCGCTACATTGTTGTGGGNGTGGAGAACCTNATNAACGCTGANTTTTGCGTGGCCT
NTGTTTGCGTGGCCTTTGGGGCAGTTTTGGGTAAAGTCAGCCCCATTCAGCTGCTNATCATGA
CTTTTTTC

FIGURE 106

GGGGAACTTGGGAGGAACATGCAGGAGTGNATTTGTTTTGGTGGGGGTTTTCCTGGCCTGGTT
CAGGCCTGCCNTGAGCCCTGGGANTGTGGGGAAAAGTATGGTTTCCAGATNGCCGACTGTGCC
TACCGNGACNTAGAATCCGTGCCGCCTGGTTCCCGGCCAATGTGAATACACTGAGCCTGTCAG
CCAACCGGTGCCAGGCTTGCCGGAGGGTGCCTTCAGGGAGGTGCCCCTGCTGCAGTNGCTGTG
GCTGGCACACAATGAGATCCGCACGGTGGCCGCCGGAGCCCTGGCCTTTTTGAGCCATTTCAA
GAGCCTGGACCTCAGCCACAATTTNATTTNTGANTTTGCCTGGAGCGACCTGCACAACCTNGT
TGCTGTCCATTTTGAG

FIGURE 107

CCCAAGGGTNCGAAATTTGGAANGTTCATAGGTTCTTCAANGTCCTTCATTCCCTGGTAGACA
AATCCAANATCAACCGACAGTTGGAGGTATANACAAGCGGAGGGACCCTGAGAGTGTGGCTGG
GGAGTATGGGCGGCATTCCTTTTACAAAATGNTTGGTTANTTCAGCCTGGTCGGGTTTTTCCG
CCTGCANTCCCTGTTAGGAGATTACTACCAGGCCATCAAGGTGCTGGAGAACATCGAACTGAA
CAAGAAGAGTATGTATTCCCGTGTGCCAGAGTGCCAGGTCACCACATACTATTATGTTGGGTT
TGCATATTTGATGATGCGTTGTTACCAGGATGCCATCCGGGTTTTNGCCAANATCCTCCTTTA
CATCCAGAGGACCAAGAGCATGTTCCAGAGGACCANGTACAAGTATGAGATGATTAACAAGCA
GAATGAGCAGATGCATGCGCTGCTGGCCATTGCCCTCACGATGTACCCCATGCGTATNGATGA
GAGCATTCACCTCCAGCTGCG

FIGURE 108

GACCCATCCCANGNGTCCGGAGATCATGAGGATGTTTTTTAATGGCCGGTACATCCTCCTGCT
GATGGGGCTGTTTTCAGTGTACACTGGCTTCATTTACAACGATGCTTTTCAAAGTCAGTCAAC
CTGTTCGGNTNTGGGTGGAACGTGTCGGCCATGTACAGNTCCAGCCACCCACCCGCAGAGCAT
AAGAAGATGGTGCTTTGGAACGACAGCGTNGTTAGACACAACAGCATTTTGCAGCTGGATCCA
AGCATTCCTGGAGTGTTCCGAGGCCCTTATCCCCTTGGCATTGATCCTATTTGGAANTTGGCC
ACAAATNGCCTCACTTTTNTAAANTNTTTCAAAATGAAAATGTCCGTGATTTTAGGAATCATT
NATATGANTTTTGGAGTCATTTTGGGNATATTTAACCANTTGCANTTCAGGNAGAAGTTCAAC
ATTTACCTGGTTTCCATCCCGGAANTTCTTTTCATGCTNTGTATTTTTGGATACCTA

FIGURE 109

TAAGGCCTTCAGGTCCCCTTCCTTACCCCAGGTTTTTCACAGAATGGATTCCCAGCGGGAAAT
TGCAGAGGAANTGCGGCTTTACCAATCCACCCTTTTTCAGGATGGTNTAAAAGATTTCCTGGA
TGAGAAAAAATTNATNGATTGCACCCTAAAAGCAGGGACAAAAGTTTTCCTTGCCACAGATTG
ATTTTGTCAGCTTGTAGTCCTTANTTCCGGGAGTACTTTTTATNTGAAATTGATGAGGCGAAA
AAAAAGGAGGTAGTGCTAGACAANGTGGATCCTGCTATANTTGATTTAATCATCAAATACCTG
TACTNTGCCAGTATTGATCTCAATGACGGAAANGTGCAAGATATTTTTGCATTGGCCAGCCGC
TTTCAGATCCCCTCAGTGTTTACTGTNTGCGTTTNTTATNTTCAGAAAAGANTTGCTCCTGGT
AACTGTNTAGCCATCCTAAGATTAGGANTTTTTTTTGACTGCCCGAGANTNGCCATTTNTGCC
CGTGAANTTGTGTCTGATCGCTTTGTACAGATTTGTAAGGNAGAGGANTTTATGCAACTGTTT
CCACAG

FIGURE 110

GCATTATTTGAATGCAGCATGGCAGCTATTATCACCTTAATTGGGAGTGATCCCAGGNGGGGT
TCTTTATATTCGTTCATGTCGAGTATTGATGCTTTCTGACTGGTACACGATGCTTTACAACCC
AAGTCCAGATTACGTTACCACAGTACACTGTANTCANGAAGCGTTTACCCACTATATACCATT
GTATTTATTTATTACGCATTNTGCTTGGTATTAANGATGCTGCTCCGACCTCTTNTGGTGAAG
AAGATTGCATGTGGGTTAGGGAAATNTGATCGATTTAAAAGTATTTATGNTGCACTTTACTTT
TTCCCAATTTTAACCGTGCTTCAGGCAGTTGGTGGNGGCCTTTNANAAAANGCCTTCCCATAC
ATTATATTAGTGTTATNTTTGGTTANTCTGGCTGTGNANATGTCTGCTTTTGAAATAGAGAAC
TGCTATGATTTTNTGGTCAGAAAGAAAAGANTTATTGTTNTTTTCAGCCACTGGTTANTTCAT
GCCTATGGAATAATTTCCATTTCCAG

FIGURE 111

GGTCACTGTGAGCAGGTGGTATTNACAGCCTGCATGACCCTNACGGCCAGCCCTGGGGTGTTC
CCCGTCACTGTACAGCCACCGCANTGTGTTCCTGANANGTACAGCAACGCCACGCTTTGGTAC
AAGATTTTCACAACTGCCAGAGATGCCAACACAAAATACGCCCAAGATTACAATCCTTTCTGG
TGTTATAAGGGGGCCATTGGAAAAGTTTATCATGCTTTAAATCCCAAGCTTACAGTGATTGTT
CCAGATGATGACCGTTCATTAATAAATTTGCATNTCATGCACACCAGTTANTTCCTTTTTGTG
ATGGTGATAACAANGTTTTGCTATGCTGTTATCAAGGGCAG

FIGURE 112

AAGGGTCCGGTTGGTTCATTTAANGTATATTAAATTGAAAGGGTTNCTTTCAGTCATTGGAAC
AGTTTGTATNATTGGGAACACCCAACCNATGTTAGTAGGATGGGATGTGTTACAGTGTGTTTA
ANACATTNTAAATTACAGNGCATGNGCTTATGTCCGTTGGTTATTTGTTGAGCAGTAAATTTA
GGNGGAATATTTTTTNTATTTTCCTCNANGGGATAGGCAAGCTGTGGGGNAGCACAGGCTTTG
GAGCAAGCAGATTTGATTGTGACCTTATATAAGTTTCAATTTCCCTGTCTGTAATTAGATCCC
CACTTTATTGGGTTGTTGTAAGGATTAAATGAAGTAATTTNTGTAAAACATAATGACTGATAC
AAAGTAGNAAATAAGTAAATTTTTAATTTTNTTTCANTTTTGCACCAGCATACAGACATAGTA
TGTTTCNTTTTGACCAAACAGAACAGAATNAGATGTGTAATAATATAAGAGTGANTTAGCAGT
TNTAGTTATTTACCTAATAGAAATGAGTGCATATGTGTGCCAGAAGACATGTATAGGNATGTT
NATAGCAGCATTGCTTGTGATAGCCCAAAAANTAGAAACACCCACAGATTTAACAACAGTAGA
ATGGATTAATAAATTGTGGTATATTCATAAAATGCAATTTNATTNAACAACAGNAGCGAACAC
AGTANTGGTACACACACC

FIGURE 113

GCTGGAAATATGGATGTCATCTACGAGAAACTGTTTTAAGCCACAGACAATTAAAAGACCTTT
AAATCCTTTGGCTTCTGGTCAAGGGACAAGTGAAGAGNACACTTTTTACAGTTGGCTAGAAGG
TCTCTGTGTAGAAAAAAGAGCATTCTACAGACTTATATCTGGCCTACATGCAAGCATTAATGT
GCATTTGAGTGCAAGATATCTTTTACAAGAGACCTGGTTAGAAAAGAAATGGGGACACAACAT
TACAGAATTTNAACAGCGATTTGATGGAATTTTGACTGAAGGAGAAGGTCCAAGAAGGCTTAA
GAACTTGTATTTTCTCTACTTAATAGAACTAAGGGCTTTATCCAAAGTGTTACCATTCTTNGA
GCGCCCAGATTTTCAACTNTTTACTGGAAATAAAATTCAGGATGAGGNAAACAAAATGTTACT
TTTGGAAATACTTCATGAAATCAAGTCATTTCCTTTGCATTTTGATGAGAATTCATTTTTTTG
CTG

FIGURE 114

CCTTGAAAATTATGGTGTGGCCGGAACCAAANAACTTTGCTTTATTGGGGACTGGGCNTTNAA
GTTTCCAGGGGCACCTTTTGGNGCCAGCCCCATGCAGGGGATTTTTGGAAGTGTGCAGGTGCC
TGTATGGTTCAGTACCAGAAGTNTTTTGTGGCTTTTGAAGTTNGAGGCAAGGCCTGGGTGCCC
AGGCCGGTGCCCGCNTGGGGTTCAAGCGGACCAGTTCCATGGATTCCCCAGGAGGTCCCCTGC
CCNTCCCCNTGTTCAAAGGAGGGGTTGGCGGTGCAGGGGCAACCCCTNGAAAGCGGGGTGTTT
TNTTTTTTNTNGANGCCTTCCGGGTGAAACCCTTTTTGNTCCATATGCCCTAAAATTATTTGG
GAAGGCTGGGGAAGTAGGNTTTGGGTCCATGCCTAAATTTGTACCGTTTTATTCCTCAAGGCC
TATAGCCTGTCAATCCTTGAAGCCTTTTTTGCCTGTCCCTCCGATCCTTGTCCACCGTTTATT
TATTGCCCAATTTATTGTTTATACGGATGANTGGGAGGCAATGCACC

FIGURE 115

GCAGAGGTTGAGCGGCAGAAANATAAAACCCTTGAAAGTGCCTTCCCTGGNTCCAGCCATCAT
CNTCATCCTCCCTGGGGTCGTCANGTTCATGGTNTCCTTCATTGGTGTGCTGGNGTCCCTCCC
GTGACAACCTGTACCTTTTCCCAAGCATTCANGTACATCCTTGGGATTTGCCTNATCATGGAG
CTCATTGGTGGNGNGGTGGCCTTGACCTTCCGGAACCAGACCATTGANTTCCTGAACGACAAC
ATTTGAAGAGGAATTGAGAACTACTATGATGATTTGGANTTCAAAAANATCATGGANTTTGTT
CAGAAAAAGTTCAAGTGCTGTGGCGGGGAGGANTACCGAGATTGGAGCAAGAATCAGTACCAC
GANTGCAGTGCCCCTGGACCCCTGGC

FIGURE 116

GTCATTTCCCCCGCTTTTATATCCTGTACACAATTTTCATGAAAGGATTGCAGATGTTATGGG
CTGATGCCAAAAAGGGTAGAAGAATAAAGACAAATATGTGGAAGCACAATATAAAGTTTNATC
AANTTCCATACCGGGAGATGGAGCATTTGAGACAGTTCCGCCAAGANGTCACCAAGTGTNTTT
TCCTAGGTATTATTTCCATTCCACCTTTTGCCAANTACCTGGTTTTTTTGCTAATGTACCTGT
TTCCCAGGCAAATANTGATCAG

FIGURE 117

GGGTGGAATCCCAATTTTTGGGGGGAAGNTTTCCGGAGGTTCANTTAAGGGAAGNAATTTCAA
AATGAAAATTCAAAGTAGTGTTNGCCCAGAGTTGATTGTGGTCAGCATTTNGANATAGCCCAG
AGATACAGGATAAGCAAATACCCAAACCTTNAAATTGTTTNGTAAATGGGATGATGATGAAGA
GAGAATANAGGGTTCAGNGATCAGTGAAAGCATTGGCAGATAACATNAGGCAACAAAAAAGTG
ACCCCATTNAAGAAATTCGGGANTTAGCAGAAATCACCANTTTTGATNGNAGCAAAAGAAATA
TNATTGGATATTTTGAGCAAAAGGANTNGGACAACTATAGAGTTTTTGAANGAGTAGNGAATA
TTTTGCATGATGACTGTGCCTTTTTTTTTGCATTTGGGGATGTTTCAAAACCGGAAAGATATA
GTGGNGACAANATAATTTACAAACCACCAGGGCATTTTGNTCCGGATATGGTGTANTTGGG

FIGURE 118

AAAGCCCAAGTTACCAGCTGTTCAAAAAACAGTNGNGATTTCAGTTTCACGATTGTTGACCCG
GTGATTTCCCCAGTGCTGAACATTATGGTNATTCAAACAGNAACAGACCGACATATAACATTA
CATTGCCTTTCAGTCAATGGNTCGNTGCCCATCAATTACACTTTTTTTGAAAACCATGTTGCC
ATATCACCAGGTATTTCCAAGTATGACAGGGAGCCCGAACCCCTTGC

FIGURE 119

ATATGCAGAGAGACTGGGTGNTCCGAGCTCCANTCAGGTGAAAGAATTTGCGGCAATTGTTGA
NGTGAAAGGAGAATTTCATTACATTTTGGATCCAAAGCAAGCACTGATGAAGCTCACCCTAGG
TANTGCAGGCAGTTTATTTCCCCAAGCATTGTACATTTTGNTTGANTTCATATGGAGTTTTTT
ATTCAAAANTTCAGC

FIGURE 120

GTTATTGTGAACTTTGTGGAGATGGGAGGTCNTGGGGCTGTGTTCCATGGCGAGCTGGATACC
ANGTTTGTGTGGAAGTGCCCCGTGTTTGNTATGCCGATGCTGTCCTAGTGGAAACAANTCCAC
TGTAATTAGATTGATNTATGCACTTTTNTTGCTTGTTGGAGTANGTGTAGCTTGTGTAATGTT
GATACCAGGAATGGAAGAACAACTGAATAAGATTCCTGGATTTTGTGAGAATGAGAAAGGTGT
TGTCCCTTGTAACATTTTGGTTGGCTATAAAGCTGTATATNGTTTGTGCTTTGGTTTGGCTAN
GTTCTATNTTCTTCTCTCTTTACTAATGATCAAAGTGAAGAGTAGCAGTGATCCTAGAGCTGC
AGTGCACAATGGATTTTGGTTTTTTAAATTTGCTGCAGCAATTGCAATTATTATTGGGGC

FIGURE 121

TGGAGATAAGAGGTTACAGCAAATTACATGATGACCTAGGAGAGTTTCCATATGGATNGTTTG
AANTTGTNGCTAGTANAAAATCTTTCCTNTTTTTCACTGACATGTTNATTTANTGGATTCACA
GAGGCCTTCATNATAGACTGGTATATAAGCGCCTANATAAACCTCACCATATTTGGAGATTCC
TANTCCATTTGCAAGTCNTGCTTTTCACCCTATTGATGGC

FIGURE 122

TGCGCCTGGCCTGATGGTTCANTTTTTTTTAAANTTTTTTATCAGTACAAATTATGGGATAAC
ATATGAAATTTTATTATGTGTATGTAATGCATAGTGATAAAGTCAAGGTATTTACGGTGTCCA
TAACCCAAATACAATACATTTTTGTAACTATAGTCACCCTGCTTTTTTATCAAACATTGAATT
TATTCCTTNTATNTTATTTATGTGTGTANTTTTTAACACANTTCTCTTCATCTTCCCTTCTCC
TCCCAATCACCCTTCCCGTCC

FIGURE 123

AGAAGGGGGGGTGAAAGTGGTTGCCCAGTAATGGCCAGAAACCAACCACCAGAGGCCAGGNTG
AAAGACAAGNTCCGGGTGTCCTGGGGCTGACGGGCCAACCATGTGGCAGGTCCCAGGCCCCAC
CCANTGCGCCATCCGCCTTTGAGCTCCACAGTGGTCCCACTAATGGGAACCTCCTTTAGGGAG
AGTGATACTGCACCTTCACCCGTAGGAATNATATTTATAACAATGTGTAATGGCTGTAGCAAA
AAGCCCTTGTTTTTAGATGTAAATGGTCAAAGAAACAAGCGCTTTATTGTTTTGAATAAAATA
GTTCAAATGAGTCCTGTATCATTGTATNTCCTATTNTGGATTAGTGCCTTTTGGACGATTG

FIGURE 124

ATGGAAAATTTTTTTTAGGGGGGGGTGGTTCNTGAGCGAAGGTGGGCGGACGNGNGGGGGATT
TTTTTNTGGCCCTGTTCCTTCNGAGCGTTCCGCCGTTGCCCGCCTGGCCCCTACGGAGTCNTT
AGCCAGGATGGAGGCTGTTGTGAANTTGTACCAAGAGGTGATGAAGCANGCAGATCCCCGGAT
CCAGGGNTACCCTTTGATGGGGTCCCCCTTGCTAANGACCTCCATTTTCCTGACCTANGTGTA
NTTTGTTTTNTCANTTGGGCCTNGCATCATGGCTAATCGGAAGCCCTTCCAGCTCCGTGGNTT
NATGATTGTTTACAANTTNTCACTGGTGGCANTNTCCCTTTACATTGTTTATGAGTTCCTGAT
GTCGGGCTGGCTGAGCACCTATACCTGGCGCTGTGACCCTGTGGAATATTCCAACAGCC

FIGURE 125

AAGTAGGGAAGTGTATTTCCAGNTACAGATTTGATCCCGTTGGAGTGGATATCACTTCGAAAG
GAAAAATGAGAGCAAGATATGTGAATTACATCAAAACATCAGAGGTTGTCAGACTGCCCTATC
CTCTCCAAATGAAATCTTCAGGTCCACTTCTTACTTTATTAAAAGGGAATNGTGGGGCTGGAC
AGACTTTCTAATGAACCCAATGGTTATGATGATGGTTNTTCCTTTATTGATATTTGTGCTTNT
GCCTAAAGTGGTCAACACAAGTGATCCTGACATGAGACGGGAAATGGAGCAGTCAATGAATAT
GCTGAATTCCAACCATGAGTTGCCTGATGTTTCTGAGTTCATGACAAGACTNTTNTCTTCAAA
ATCATTTGGCAAATTTAGCAGCGGCAGCAGTAAAACAGGCAAAAGTGGGGCTGGCAAAAGGAG

FIGURE 126

CTTTCCCCCTGGCGGTGAGAGTGCAGAGACGAAGTGCGAGATGAGCATTATGTTCGCGGACAT
CTCCTCATCGTTTTTATCTCNGNGTGCACGGTNTGTTNGCAGAGGGCANAACCTGGGTCCTGG
TTTACAGGACAGACAAGTACAAGAGANTGAAGGCAGAAGTGGAAAAACAGAGTAAAAAATTGG
AAAAGAAGAAGGAAACAATAACAGAGTCAGNTGGTNGACAACAGAAAAAGAAAATAGAGAGAC
AAGAAGAGAAACTGAAGAATAACAACAGAGATTTATCAATGGTTNGAATGAAATCCATGTTTG
TTATTGGCTTTTGTTTTACTGCCCTAATGGGAATGTTCAATTCCATATTTGATGGTAGAGTGG
TGGCAAAGCTTCCTTTTAC

FIGURE 127

ATTTTTTTAGTATATCCACAGAGTTGTGCAACCATCAATTTTAGAACATTTTCATCACAAATT
TTGNGCNTGTAATAGTTTCCTAGAGCTGTTTNTTAACGAAGTACCACAAGNTGGGTGGCTTAA
GACAACAGAAATGTATTCCTGGCCGGGTGCAGTGGCTCACGCCNGTAATCCCN

FIGURE 128

ATTTCCCTTCCTTTTTTCCCGCCCNGTATTTTTTTNAACCTTTTTCCCACCTTTGNTTGGGT
AGCCATGGGGGGAGCCGTNGGGGGCAATCAGTCCCATTCCATTTCCTTGTTGTCCNTTGGGAG
CCGAGCCGTTCCGCGCCCGGTGGNGGCGGGAGCCCAGGAGCCTGCCCNGCCTGGGGANGAAGA
GTGCAGTTCTTCNTGGCGGTGCACGATNTGATTTTNTGGAGAGATGTGAAGAAGACTGGGTTT
GTTTTTGGCACCACGCTGATCATGCTGCTTTCCCTGGCAGCTTTCAGTGTNATCAGTGTGGTT
TCTTACCTCATCCTGGNTTTTCTCTCTGTCACCATCAGNTTCAGGATTTACAAGTCCGTNATC
CAAGCTGTACAGAAGTCAGAAGAAGGCCATCCATTCAAAGCCTACCTGGANGTAGACATTAAT
TNTGTCCTCAGAAGCTTTCCATAATTACATGAATGCTGCCATGGTGCANATCAACAGGGCCCT
GAAANTCATTATTTGTCTNTTTNTGGTAGAAGATTTGGTTGANTCCTTGAAGCTGGC

FIGURE 129

TGTTCCTCAATCCAATTTCCGGATTTTAGAATGCCCGTAAAAAATTTATAATTTTANTNTCAA
GAAANATTTTACCAGGGGCAATTGTAAAGGTTTTATTAATTTTTAACCTTTGGCCTTTTTTTT
TAAGTAAGGCAATTAATATAAATGTAAAATATACAATATTAACAAACNTGGTTTCCAGNTTGT
ACATTTAGTAAATATTTAATATTAATTACGAGTTATTGAGGTTTAAAGTAGGCTGTGCATGTG
TAATTATATTTTATTATGTTCAGTTTTCCATGGCAATTGCCTAGTTTTTAAAGTTTATTATAA
TCCTTATGTTTGTGATNTTTTTTCATANTTTATTATTTACAGGAGTCCAGNTANTTGCTNTTT
TAGTTCCCANTTTGATATTTTACCTGNTGGATGAAAATTTTTTTGCCTCAGCAAGTTCAGCTT
CCAAAGATTTTCATGAGTTTGCANTCCAGAATTTAATGCATATTGGACCTNTGTATCCACATG
CTTTCAAGACAGTAATGGGGGC

FIGURE 130

AAATAAATTTTTCATCCCATTATGCATTTTGTTTGTAAATGTAAATTTTAAAAATATGGTTAA
TAACATTTCAACCTGTTTATTACAACTTAAAAGGAATTCAGTGAATTTGTTTTTATTTTTTAA
CAAGATTTGTGAACTGAATATCATGAACCATGTTTTGATACCCCTTTTTCACGTTGTGCCAAC
GGAATAGGGTGTTTGATATTTTTTCATATGTTAAGGAGATGCTTCAAAATGTCAATTGCTTTA
AACTTAAATTACCTNTCAAGAGACCAAGGTACATTTACCTCATTGTGTATATAATGTTTAATA
TTTGTCAGAGCATTNTCCAGGTTTGCAGTTTTATTTCTATAAAGTATGGGTATTATGTTGCTC
AGTTACTCAAATGGTACTGTATTGTTTATATTTGTACCCCAAATAACATCG

FIGURE 131

GGGGGGGGTGAAAGTGGCTGCCAGTAATGGCCAGAAACCAACCACCAGAGGCCAGGCTGAAAG
ACAAGCTCCGGGTGTCCAGGGGCTGACGGGCCAACCATGTGGCAGGTCCCAGGCCCCACCCAN
TGCGCCATCCGCCTTTGAGCTCCACAGTGGTCCCACTAATGGGAACCTCCTTTAGGGAGAGTG
ATACTGCACCTTCACCCGTAGGACTCATATTTATAACAATGTGTAATGGCTGTAGCAAAAAGC
CCTTGTTTNTAGATGTAAATGGTCAAAGAAACAAGCGCTTTATTGTTTTGAATAAAATAGTTC
AAATGAGTCCTGTATCATTGTATCTCCTATTNTGGATTAGTGCCTTTTGGACGATTG

FIGURE 132

GGATATCTTTTTCCATCCCTTTATTTTCAGTCNATGNGTGTCTTTATAGGTGAAATGNGTTTC
TTGTGGGCAACAGATCAATGGGTCTTGTTTTNACATCTATTCAGCCAGTCTATGTCTTTTGTT
TGGAGAGTTTAGTCGATTTATGGTCAANGTTATTATTGATAAGTAATGATTTCTCCCAGTTTT
TTTTCTGGTTGTTTNGTGGTCTTCTCTTCTTTCTTTCTTTCTTTCTTTCCTTCCCGCTCCCAG

FIGURE 133

GTATGTACATGTGTATGGTGTGTGCATGTAGGTGTGGTGTGCGTGTGCGTGGTGTGNGTGCAT
GTGTATGTGTGTGGCATGTATGTGTACGGTATGTATATGTGTGGTGTGTGTGCANGTGTGTGT
ATGTGTGTTTTTG

FIGURE 134

GGGGAAAAATATCTGTTACAAATTTATAATTTCAAGACAAATTGAATCTTATTTTATAATACT
TTTGGAATTTCATTAATAAGGCTAAAATTTGAGGAATATAAATAATTTTCAGCCTTAAGACAT
NTAAGTTTGGAAGTCCTTGCTATTCAACAGAATAACAAGAAAACTTCAGAATGTATCACTNTC
CTGAAAAGAAGATATTAATAAGCCCTTTTATTTATGGTTATAGTTTTATTTATAGTCTCAAAA
TTCCTAAAGCAATGCTACAACCATTGAATTTGCCATATTTTGTATCAGTGCTGTTAATTTGCT
GTTGCCTCAAGAAAAAGTGCTTTTTCTCCATGGATGAGGCTAGACCCTCGN

FIGURE 135

AGGGGGTTCTTGACATTTTGTTCAAATCCTNGTAACAATCTGTCTTTAGCTTTATTTTNTGAG
AAACTGAGCAAACCTGTTTCCATTGCCTTCTTAGAAGGGTTCATGTATATAGCACTACAGAAG
CATAATGAAGTTTCTCAGCTCCCAAAATTATNGTTATTATACTGCTATTATAC

FIGURE 136

TATTCGCGATTGACTCCTCTTNCTAAGTGTCGCGCCCCNTTTAGAGCAGCGATNTAAGAGAGC
CGTCCCGGTGTCCTCGGGTCCCAGTGATTGTGAAGTGCTGCCAATTGCCACTGGACATACTTG
AAACAAAATAGGAAAATGGCAGCAAACTCTTCAGGACAAGGTTTTCAAAACAAAAATAGAGTT
GCAATCTTGGCAGAACTGGACAAAGAGAAAAGAAAACTACTTATGCAGAACCAGTCTTCAACA
AATCATCCTGGAGCTAGCATTGCACTCTCGAGACCCTCTCTTAATAAGGACTTCCGGGATCAC
GCTGAGCAGCAGCATATTGCAGCCCAACAGAAGGCAGCTTTGCAGCATGCTCATGCACATTCA
TCTGGATACTTCATCACTCAAGACTCTGCATTTGGGAACCTTATTCTTCCTGTTTTACCTCGC
CTTGACCCAGAATGAAGAAAACATTTGCGATGGAAAAGTGAC

FIGURE 137

CTTGAGCGAGCCAGTTGCCGGATTATTCTATTTCCCCTCCCTCTCTCCCGCCCCGTATCTCTT
TTCACCCTTCTCCCACCCTCGCTCGCGTAGCCATGGCGGAGCCGTCGGCGGCCACTCAGTCCC
ATTCCATCTCCTCGTCGTCCTTCGGAGCCGAGCCGTCCGCGCCCGGCGGCGGCGGGAGCCCAG
GAGCCTGCCCCGCCCTGGGGACGAAGAGCTGCAGCTCCTCCTGTGCGGTGCACGATCTGATTT
TCTGGAGAGATGTGAAGAAGACTGGGTTTGTCTTTGGCACCACGCTGATCATGCTGCTTTCCC
TGGCAGCTTTCAGTGTCATCAGTGTGGTTTCTTACCTCATCCTGGCTCTTCTCTCTGTCACCA
TCAGCTTCAGGATCTACAAGTCCGTCATCCAAGCTGTACAGAAGTCAGAAGAAGGCCATCCAT
TCAAAGCCTACCTGGACGTAGACATTACTCTGTCCTCAGAAGCTTTCCATAATTACATGAATG
CTGCCATGGTGCACATCAACAGGGCCCTGAAACTCATTATTCGTCTCTTTCTGGTAGAAGATC
TGGTTGACTCCTTGAAGCTGGCTGTCTTCAT

FIGURE 138

CCTTAGCAGACATGCAAAAGCTTATTCTTGTGTGACTTACTTTCTTTAAGCTAATAATATAAA
AATAAATATGTATCTTAAAAATCTATAATAAAACATTAGAAATTAAAGATATGTGCTTTTTAT
TTTGCAGATGAGTTCATTTGCTTTTGTAGATGTGTTTTCAGAGCTAGGTACAGAGGAATGTTT
GCTACCTTTAGCGGTGAAAAAAGAAAGAGAGTCAAGAATTTTGTTGGATTGTGTTTGTGTGTG
CATATATTTGATATCATCATTATATTTGTAATCTTTGGACTTGTAATCATAGCCTGTTTATTC
TACTG

FIGURE 139

CGGACGCGTGGGCTGCTTGCCGCCCTCTTTGGATACCTAACATTTTACGAACATGTTGAGTCA
GAATTGCTTCATACCTACTCTTCTATCTTGGGAACTGATATTCTTCTTCTCATTGTCCGTCTG
GCTGTGTTAATGGCTGTGACCCTGACAGTACCAGTAGTTATTTTCCCAATCCGGAGTTCTGTA
ACTCACTTGTTGTGTGCATCAAAAGATTTCAGTTGGTGGCGTCATAGTCTCATTACAGTGTCT
ATCTTGGCATTTACCAATTTACTTGTCATCTTTGTCCCAACTATTAGGGATATCTTTGGTTTT
ATTGGTGCATCTGCAGCTTCTATGTTGATTTTTATTCTTCCTTCTGCCTTCTATATCAAGTTG
GTGAAGAAAGAACCTATGAAATCTGTACAAAAGATTGGGGCTTTGTTCTTCCTGTTAAGTGGT
GTACTGGTGATGACCGGAAGCATGGCCTTGATTGTTTTGGATTGGGTACACAATGC

FIGURE 140

ACTTCAATGTNTACACATGGCCATTGAAAAATACAGAGTTTACAGAATTATTTCAGAGAAGTC
ATTAAAGAAACAAACATTAACACACCCTGCAGAGTGGGGGAG

FIGURE 141

TCCCCGCTGCTGACGCTTCATCCCCCACACCTCCAGCCCCAGTTACCTGGAGCTTCTCAGAAC
CCACTTTGCCGGTGCTAAAACACAAGAGGGGGTGAAAGTGGCTGCCAGTAATGGCCAGAAACC
AACCACCAGAGGCCAGGCTGAAAGACAAGCTCCGGGTGTCCAGGGGCTGACGGGCCAACCATG
TGGCAGGTCCCAGGCCCCACCCACTGCGCCATCCGCCTCTGAGCTCCACAGTGGTCCCACTAA
TGGGAACCTCCTCTAGGGAGAGTGATACTGCACCTTCACCCGTAGGACTCATATTTATAACAA
TGTGTAATGGCTGTAGCAAAAAGCCCTTGTTTCTAGATGTAAATGGTCAAAGAAACAAGCGCT
CTATTGTTTTGAATAAAATAGTTCAAATGAGTCCTGTATCATTGTATCTCCTATTCTGGATTA
GTGCCTTTTGGACAGTAGACTGTTCTGTAAAA

FIGURE 142

TCCATGTGAATTTTGCTTAATGGAATGCTTTATTTAAGCATTTAGGCAGAGTTGACACANTTA
AAGGTACAAAGCCCAGAGGAATTGGTAGAGCAGCACCGTGCNTGCCNTGAGGCAGTGGAGTCA
GTAGCGTTGTCCCCAGGGCCTTGAGTGCCTGGAGGTGCTTGGCCTCCAGTAGCTGCCTCCATT
CTCTTTTAAAAAAAGGGGGTGATTCTGAGGCACTGAAGTGCCTCCCAGATGTGGAGGAGTGAA
GCCACCATCGAGGCCACACTCAGCACTCCAGGATCCCAGCGATGTCAGACACTCTTGAGTTGT
CAAAACGTTAATTTTCAGTTTTAAATAATCAGTTTATCTAAGAAAAGGGAATTTTAACTTTTC
TACCTTGAGCCAAGCCAATGAAGGGAAAATTAATTAACTTAGTAAATTTGAAGTGCAGCTCTG
TTAGCTCGTACATGTGGGTTCTTATCCTGATCCTGTGCCTTAAAGTAGGAAGGTGTTTCCAAG
TTCAGATTAAAATAGAAGCAGCTGGCCGGGTGCGGTGGCTCACGCCTGTAATCCCAGCACTTT
GGGAGGCCGAG

FIGURE 143

CAAGAGTCTCGCTCCAGCCTGGTGATAGAGCAAGACTCCGTCTAAAAAAAAAACCAGGAGTGA
NAAAAATAAGAGTCATTGAACTTCATTTTTTTAAAAAAGAATATCACTTTGCTGTCCTTTCAA
ATATAGCATTTCCCCAATTAGGTACCTGTTTATTGAGATTTTATAATGTAGGTAAATTTTTAA
TCAGTTTTTAATTGATACCTAATTAACCTCGAGCTCTTGTCCTCCTGCCTTTTTTCACTTCTT
TACTCTTGCAGCATTCCTTCCTAGTACCTTCTGTATGTACACTACGTTGATAGCCATGACTGG
ATGGTATATGGACAGGACTTCCATTGCTGTGCTGGGAGTAGCAGCTGGGGCTATCTTAGGCTG
GCCATTCAGTGCAGCTCTTGGTTTACCCATTGCCTTTGATTTGCTGGTCATGAAACACAGGTG
GAAGAGTTTCTTTCATTGGTCGCTGATGGCCCTCATACTATTTCTGGTGCCTGTGGTGGTCAT
TGACAGCTACTATTATGGGAAAGTTGGTGATTGCACCACTCAACATTGTTTTGTATAATGTCT
TTACTCCTCATGGACCTGATCTTTATGGTACAGAACCCTGGTATTTCTATTTAATTAATGGAT
TTCTCAATTTCAATGTAGCCTTTGCTTTGGCTCTCCTAGTCCTACCACTGACTTCTCTTATGG
AATACCTGCTGCAGAGATTTCATGTTCAGAATTTAGGCCACCCGTATTGGCTTACCTTGGCTC
CAATGTATATTTGGTTTATAATTTTCTTCATCCAGCCTCACAAAGATGAGAGATTTCTTTTCC
CTGTGTATCCACTTATATGTCTCTGTGGCGCTGTGGCTCTCTCTGCACTTCAGAAATGTTACC
ACTTTGTGTTTCAACGATATCGCCTGGAGCACTATACTGTGACATCGAATTGGCTGGCATTAG
GAACTGTCTTCCTGTTTGGGCTCTTGTCATTTTCTCGCTCTGTGGCACTGTTCAG

FIGURE 144

AATTGGTAGTCCCTGTTCTTTTCATGGTTTTCTGGCTCGTCTTATTTGNTCTTCAGATTTACT
CCNTATTTCNAGTACTTNGAGATCAGCNTGCATAACGTGAGAGGTTTCTTTTCCTTTTTCTGA
CAAGTATTGCGGAATGTTGCAGCAACTCCTTACTCTCTTTTGGGTTTGGTCTTCACGGTTTCT
TTTGTTGCCTTGGGTGTTCTCAACACTNTGCAAGTTTTACTTGCAGGGTTATCGAGCTTTCAT
GAATGATCCTGCCATGAATCGGGGCATGACAGAAGGAGTAACGCTGTTAATCCTGGCAGTGCA
GANTGGGCTGATAGAACTGCAGGTTGTTCATCGGGCATTCTTGCTCAGTATTATCCTTTTCAT
TGTCGTAGCTTCTATCCTACAGTCTATGTTAGAAATTGCAGATCCTATTGTTTTGGCACTGGG
AGCATNTAGAGACAAGAGCTTGTGGAAACACTTCCGTGCTGTAAGCCTTTGTTTATTTTTATT
GGTATTCCCTGCTTATATGGCTTATATGATTTGCCAGTTTTTCCACATGGATTTTTGGCTTCT
TATCATTATTTCCAGCAGCATTCTTACCTCTCTTCAGGTTCTGGG

FIGURE 145

AAAAAAAAAAAACCAAAACCAAAAACCAGAACGCTTGTTCAAGTTTGTCCTGTCCTGTCCATGG
ATAGGCCAGACCTTTGGTCCAGAAATTCAGTTTTTCATTGTGTCTGACATAGNGACTCCATAA
TGTTGGTTCCATTCTCTTTTCTTCCTCAANATCATGTGTTTTGTGGGTCTTTGTTTTGTTTTG
TTTTGTTTTGTTTTGTTTTGTTTTTGGTAGAGTTGGAGTCTTGCTGTGTTGCCCAAGNTGATN
TCCAATTCCTGACCTCAAACAGGTNTNTCACCTTGGCCTNCCAAAGTGNTGGGAATTCAGGNG
TGAACCACCTCACCCAGCCAAGNTCACATTTTGAATCTAANTTTTTTTTTGAAACAGTGTCTT
GCATTGTTGCCCAGGCTGGAATGCAGTGGTGCCATCATGGCTCACTGCAGCCTCAACTTCC

FIGURE 146

GGCAGTCTCCTAGCTGCTCTTACACACTGCATAGCTGTGTGAGTACTCTTTTCATCCATCA
GTCAGCCAGGGTTTGCAGGACAGATCCGGCAAGTGGTGCCCTGTATGAGGAATGCTGCAACGG
ATCTGGACTGAACCCNTCAAAAATAAAGTGATTGCTCAGTCCTCTTTGGATTTCTGCGCGACA
TATGAAACCATACCATGGCATGGCTGGAACCCAACCCGGTACCAAAAATAAAGGAAATGACCC
TGCAGGACCTGCAGCCCCAAAACGATGCGGCTTCCTCGGACGACACAGGCCCCGGACATTATG
CTGAAGAAGACAACTCAGGAAGCTGAGCAAATCCTGCTCCAGACACAAACACCATTCACTCCA
GATAATCTGTTCCTTGCTATGCCCTCCGTTGTACATTGCAACACTCACAGGGTATTGGTTTTT
CTTATTCTCTCACTCTGCCTGCAACTCGTACCTGCTAC

FIGURE 147

TTTTTTTTTTGTGTTGTCTATAGGAATTAACTTGGGATTGTTTTGTGGGTTTTTGTTTGTTTT
AAATGTAAATTGAGAATCTTTTATAAGAAATAAAAGCATTATTGGGTGCCTTTGTTTGTAAAC
CAAAAAGTAATAAATGAATCCCTATATTTCCATTATAGTATTTATTGTATTTTTATGTTCTGA
AAATTACCCATGGAACAATATGCTTAGGATTACAGGAAGCAGTCCTTACTTACACTTCTTGTC
TGTTTTAGGTGTACTTGTTAATTC

FIGURE 148

GTTGTATACTAATCAACCATTCTGCAACCTGCTTTTCTGATTTAATCTAGAACAACCTCATTC
TTGTGTATAGTACACCTCACACCACTATATTGGCTTGGTATAATAACTTTCCAACTGGCTTTT
GTCTCAGCCATGGGCAGTTTCTTTTCTGACCATCCATCTGGCCTCAGGTTCCCCTGGAGTCTT
CCTTTCTCCAGCAGTCCTTCTCTGTCTTTGTATATCTCCAGGCTTTAGCAATACGCTCACTCT
ATTTTTCTTTTTTTGATTTCACTTTTTAAATTAAAGTATTGTAAAACTGGCTTTTTGGTGCAC
AGTTTTGAGAATTTCAGTACATGAACACATTTGTGTTCCCACCACCACAATCAAGACAGAGGG
CCGTTTTATTGTCCCCAAAGCTCCACATGCTATCCTTTCAGGTCTACTTCCTTTTTACTGTTT
TTGTAATCAC

FIGURE 149

AGAATAATTTTTTAAACACAAATTCACCATGTTTCTCTACTAACTTGGAATGCTTAATGTGTT
CCCATTGTACCTAGAATAAATCCAAACTTACTTTCCAGGGTCTGCTCTCCAAGCTGTACATGA
CCTGGCCCATAGCCACCTTTCTAAACTCGTCACATCCATTNTCCTCATTGCTCATGGTGCTGT
GGACAGTCTGGTTCCTTTCTGTTNTTCTCCACTACCAAGCTCATTCACACTGCCCCTTTTCCA
AGGCCCTTCCCTACAC

FIGURE 150

GTAGGTTAGGGTCCTTAAAGGAACTTACTTTGGATTTATTGGCAAAATTATTGTGGGCACCTT
ACCCATTGNGAAATTATTTTTAGAGGCTTGTAAAANTTTAAAGTTTAGATNTTATTTGCCTTG
NTAATNTATTTAACTTTATGGAAAGTATTTACTGCTTCTGATCAGGATTTTTTGTTTGCTGTC
AAAGTAAAAGTCACTACCAGTGTCACTATTTGNTATGGAAGCCACAAACCTTGTAGTCATTTC
TTAATTATTTTCTTTCTTTTATTTTTCCATTCCCACATTCCCTTCTCATCCCCTTTTAATTCA
TTAGCAAGTATGCTGCCAGTTCTGCTTAGTCCGTCTCTCTCCCTCCACTGGTAAACCNTAGCC
CAAACCATCTTCATCTCTTATCTGTACTAACGCAAGAGCCCCTTAACTGGTATCCCTCCTTCC
ATTTCTTGATCTACTAAAATCCATACGCCACATAGTGGCTAGAATAATTTTTTAAACACAAAT
TCACCATGTTTCTCTACTAACTTGGAATGCTTAATGTGTTCCCATTGTACCTAGAATAAATCC
AAACTTACTTTCCAGGGTCTGCTCTCCAAGCTGTACATGACCTGGCCCATAGCCACCTTTCTA
AACTCGTCACATCCATTCTCCTCATTGCTCATGGTGCTGTGGACAGTCTGGTTCCTTTCTGTT
CTTCTCCACTACCAAGCTCATTCACACTGCCCCTTTTCCAAGGCCCTTCCCTACAC

FIGURE 151

TTTTGTCATTTTGAAATTTTTTTTTTTTCACCAGCCCTGAATTTTAGTTCATCCATGGATAA
ACTATTACTTTTCTTATTTTTCTTTAACTATACAATTAAGAC

FIGURE 152

TCCTTGGAACATTTTTNTAGGGATATTTCCATTTGACTTTATTAGATTAATGAAATTGGGAAA
CCTGGACGTATATNTAAACTATACTTTTTGANTATGAGCATAACCTTTTATTTCCTGTATTTT
AGAAAAAGNGACCATGTTGTGATGGCAATCATTGTGCTTNTGCATACCCAGNTGAATGTCTGT
GGAAACTCAGTTATTCTTTTAAATAGTTATTATCAGAGATATAATTATTTACAAAGTAGTTTT
TTTGTTTGTAGGTAAACTATTATAGATTTTGCTGTTCTCCCAACTGTTTTCTTGGTGTATATT
TTGAAAATATAAACCTTAAATGTTAGAACAAAGAAAACAAAAGCAAAACCCGAAAACCTTAAC
TGTGCTTGTAAACATTTAAAATATTTTTGTTAGTTTCTCTCAATTGAGTAAGAGAACCTGGCT
TTCCCACAGCAATGATCCAGGCTTTGGTAATACCCCCCTTTATGTCTCTGTACTTCTGCCATT
CTAAAGTTGATTTATTGTTTGTTACTTTTAGTGATTTTAAGTGCTCAATGAAGTTCCTTGGCT
TTCTCATGGCTTTTCATTTCCAACTAAATTACCTAGCCTTTCTTTTAATGTCTTCCACCCTTAC

FIGURE 153

TATTTAAAGCAATCTTAGTGGTATACCCCGCCCCTTTGCCTTANTTAAGAGGAGCANTGAAAT
GNATATACTTGCTGTTCAGTATTTCCAAGTACCCATTTTTATATAGTAGCTTATTTGACCATA
AGTCACACATCAAAAAAAGATTACCCCTTAGTGTATGTGTTTTAATNTTAGAAAATNTGGCAT
ATGTACTTTATTTTTGAAAAGGGAAGAGATGGGTGTGGGGTGGCAATAGCATTGTGCCATTTT
GTCATAGAATGTAAAAATTGGTTAACTTTACAAATGTCAGCTAGTTTTGACTACTAATTGGGG
GAAATTTTAGATAATTTTTAAATTCAAAGTTATTTATAAAATGCTAGAATTTGTTTTAATTTT
TTTGTATTTTGAGCCACTTCACATGAAGACTCAGTTGCATTTTTATCGAATACATTTTTATCA
ACAGTTAAAGACTATGGTGGTTTTTTTCAGAGTTTGGCTAAGAATGTTGTTACCATCTTCTTT
GTTTGTGGTACAATATTT

FIGURE 154

AATCTATTTAAACTTTATGGAAAGTATTTAACTGGNTTCTGGATCAGGATTTTTTTTGTTTGC
TNTCAAAGTAAAAGTCACTTACCAGTGTCANTATTTGGTTATGGAAGCCAACAAACCTTGTAG
TCATTTCTTAATTATTTTTCNTTCTNNTANTTTTCCATTCCCACATTCCCCTNTCATCCCCTT
TTAATTCATTAGCAAGTATGCTGCCAGTTCTGNTTAGTCCGTCTCTCCCTCCACTGGTAAA
CCCTAGCCCAAACCATCTTCATCTTCTTATCTGTACTAACGCAAGAGCCCCTTAACTGGTATC
CCTCCTTCCATTTCTTGATCTACTAAAATCCATACGCCACATAGTGGCTAGAATAATTTTTTA
AACACAAATTCACCATGTTTCTCTACTAACTTGGAATGCTTAATGTGTTCCCATTGTACCTAG
AATAAATCCAAACTTACTTTCCAGGGTCTGCTCTCCAAGCTGTACATGACCTGGCCCATAGCC
ACCTTTCTAAACTCGTCACATCCATTCTCCTCATTGCTCATGGTGCTGTGGACAGTCTGGTTC
CTTTCTGTTCTTCTCCACTACCAAGCTCATTCACACTGCCCCTTTTCCAAGGCCCTTCCCTACAC

FIGURE 155

TTTTTTATCATTTTGAACTTTATGGANAAATTGGGCAGCCAAAACGCTTCCCGGGGAAGGNGC
CAGCGAAGAATGCATCCTAACGTTAGTNAAGGNTGCCAAGGAGGNTGTGCAACATGNTCAGAT
TACAATGGATGTTTGTCATGTAAGCCCAGANTATTTTTTGTTTCTGGAAAGAATTGGCATGAA
GCAGATTGGAGTATGTCTCTCTTCATGTCCAAGTGGATATTATGGAACTCGATATCCAGATAT
AAATAAGTGTACAAAATGCAAAGCTGACTGTGATACCTGTTTCAACAAAAATTTCTGCACAAA
ATGTAAAAGTGGATTTTACTTACACCTTGGAAAGTGCCTTGACAATTGCCCAGAAGGGTTGGA
AGCCAACAACCATANTATGGAGTGTGTCAGTATTGTGCACTGTGAGGTCAGTGAATGGAATCC
TTGGAGTCCATGCACGAAGAAGGGAAAAACATGTGGNTTCAAAAGAGGGACTGAAACACGGGT
CCGAGAAATAATACAGCATCCTTCAGCAAAGGGTAACCTATGTCCCCCAACAAA

FIGURE 156

ATCNANGTGGATGCAGTCTTCATTGACANAAGTAACCTGGANATCACTCCGGACNANCCCCGC
TGGATCNGAGCCTGGTGGGGTGGCTTTCNGCTCTGCGGTGCCTTACACTTCNTCNNTTCCCTC
TTGATGTTTGGGTTTCCACAGTCCCTGCCCCCGCACTCAGACCCCGCCATGGAAAGCGAGCAG
GCCATGCTCTCCGAAAGAGAATACGAGAGACCCAAGCCCAGCAACGGGGTCCTGAGGCACCCC
CTGGAGCCAGACAGCAGTGCCTCCTGTTTCCAGCAGCTGAGAGTGATCCCGAAGGTCACCAAG
CACCTGCTCTCAAACCCTGTGTTCACCTGCATCATCCTGGCCGCCTGCATGGAGATTGCAGTG
GTGGCTGGCTTCGCTGCCTTTTTGGGGAAGTACCTGGAGCAGCAGTTTAACCTCACCACCTCT
TCTGCCAACCAGCTGCTTGGGATGACTGCGATCCCGTGTGCTTGTCTGGGTATCTTCCTGGGA
GGTCTTTTGGTGAAGAAGCTCAGCCTGTCTGCCCTGGGGGCCATTCGGATGGCCATGCTCGTC
AACCTGGTGTCCACTGCNTGCTACGTCTCCTTCCTCTTCCTGGGCTGCGACACTGGCCCTGTG
GCTGGGGTTACTGTTCCCTATGGAAACAGCACAGCACCTGGCTCAGCCCTGGACCCCTACTCGCC

FIGURE 157

TGGAAAGCCATTAAAGGAATTTAAAGTTATTTTACCTGCAGACCTGAAAAATNTATAGAACTG
TTNACATATNTTTGTATATCTNTTCANTAGGTGAACTTTTCATGGGCTAAACAGTACATTNGA
GTGAAATTCTGAAGAAACATTTTAAGGAAAAACAGTGGAAAAGTATATTAATCTGGAATCAGT
GAAGAAACCAAGACCAACACCTCTTANTCATTATTCCTTTACATGCAGAATAGAGGCATTTAT
GCAAATTGAACTGCAGGTTTTTCAGCATATACACAATGTCTTGTGCAACAGAAAAACATGTTG
GGGAAATATTCCTCAGTGGAGAGTCGTTCTCATGCTGACGGGGAGAACGAAAGTGACAGGGGT
TTCCTCATAAGTTTTGTATGAAATATCTCTACAAACCTCAATTAGTTATANTGTACACTTTCA
TTNTCATCAACACTGAGACTATCCTGTCTCACNTACAAATGTGGAAACTTTACATTGTTCGAT
TTTTCAGCAGACTTTGTTTTATTAAATTTCTATTAGTGTTAAGAATGCTAAATTTATGTTTCA
ATTTTAT

FIGURE 158

CTAATTTTATCAAAGGCCNTTTTTCCCAAAGCCATCCATCATCCCATTATTAATCTGNACTGT
TGCAACATGGCTATTGTCTGAAATTTTATGAGTTACTATCCTGGGATTTCCCTTTATCTTTCT
GTATTAGACCTTCTGTTTCTTGGAACCTATGTCATCCATCTTGATGTACTCCCTTATTTTGAT
AGTGTATATCCTTTAGTGGCTTCCTAAGAAAAAGTGCATAGATAGTAAAATTTTGAGACCTTG
CATAGCTGATAGTTTTATTCTAATCTCACTCTTGGTTGATTAGTTTAACAGGGTAGAAAATTT
CAGGTTGAATACCAGTTTTCTTCAGTATTTGAAGGTGTTATTTTATTGATTTCGAACTTTCAA
CATTGCTGTTGAAATCTGAAGTTATTCTGATTCTGATCTTTTGTATATAAGTCTTTATGACCT
CTAAAAGTTTTCAGAATTCTGTTTGTTTATGGAATTCTGAAAGTTGATGATGTACCATAGTGG
AATACTTTTACATTTATTGTACTGGGTATTCCAAAGGCCCTTTTTATCCAAAAACTCATGTCT
TTTAGTGCTGGAAATTTTTCTTTTGTTATTTTCATATTTTTCTTCCCCTTTTTTCTCTTTTCG
CTTTCTGGAATGCCTGTTGGTCAAATGTCAGATTTTCTGACTCATTCTATACAATTAGAAAGC
ACACCCAAGTTTCACTGTGGAACTACTCCAGTGAGCCCTTCAGTGTGGTCATCTCTGGGCAGA
GATACTATAGATTTACTGCTAAG

FIGURE 159

TCAGGATGTTCTTAATTGGGGAAGAAATCATTTTTTCCNTACAAAAAACCAAGCACTTCNTGG
GGCCGGATTACACTGAAACATTGTACTNACCCAGAGGAGAGGAAATTACCACGAAACCTGAGA
ACATGGAACACTGTTACTATAAAGGAAACATCCTAAATGAAAAGAATTCTGTTGCCAGCATCA
GTACTTGTGACGGGTTGAGAGGATACTTCACACATCATCACCAAAGATACCAGATAAAACCTC
TGAAAAGCACAGACGAGAAAGAACATGCCGTCTTTACATCTAACCAGGAGGAACAAGACCCAG
CTAACCACACATGTGGTGTGAAGAGCACTGACGGGAAACAAGG

FIGURE 160

ATGCTGCGTGGGATCTCCCAGNTACCTGCAGTGGCCACCATGTCTTGGGTCCTGNTGCCTGTA
CTTTGGCTCATTGTTCAAACTCAAGCAATAGCCATAAAGCAAACACCTGAATTAACGCTCCAT
GAAATAGTTTGTCCTAAAAAACTTCACATTTTACACAAAAGAGAGATCAAGAACAACCAGACA
GAAAAGCATGGCAAAGAGGAAAGGTATGAACCTGAAGTTCAATATCAGATGATCTTAAATGGA
GAAGAAATCATTCTCTCCCTACAAAAAACCAAGCACCTCCTGGGGCCAGACTACACTGAAACA
TTGTACTCACCCAGAGGAGAGGAAATTACCACGAAACCTGAGAACAT

FIGURE 161

GTTTGGGCTAACAGGATCTCCTCTTGCAGTCTGCAGCCCAGGACGCTGATTCCAGCAGCGCCT
TACCGCGCAGCCCGAAGATTCACTATGGTGAAAATCGCCTTCAATACCCCTACCGCCGTGCAA
AAGGAGGAGGCGCGGCAAGACGTGGAGGCCCTCNTGAGCCGCACGGTCAGAACTCAGATACTG
ACCGGCAAGGAGCTCCGAGTTGCCACCCAGGAAAAAAAGGGCTCCTCTGGGAGATGTATGCTT
ACTCTCTTAGGCCTTTCATTCATCTTGGCAGGACTTATTGTTGGTGGAGCCTGCATTTACAAG
TACTTCATGCCCAAGAGCACCATTTACCGTGGAGAGATGTGCTTTTTTGATTCTGAGGATCCT
GCAAATTCCCTTCGTGGAGGAGAGCCTAACTTCCTGCCTGTGACTGAGGAGGCTGACATTCGT
GAGGATGACAACATTGCAATCATTGATGCGCCTGTCCC

FIGURE 162

TGTCACAGGTGGGAAAGAAACGGACTGTGGGCCCTCTCTTGGATTAGCGGCGGGCATACCATT
GNTGGTGGCCACAGCCCTGCTGGTGGCTTTACTATTTACTTTGATTCACCGAAGAAGAAGCAG
CATTGAGGCCATGGAGGAAAGTGACAGACCATGTGAAATTTCAGAAATTGATGACAATCCCAA
GATATCTGAGAATCNTAGGAGATCACCCACACATGAGAAGAATACGATGGGAGCACAAGAGGC
CCACATATATGTGAAGACTGTAGCAGGAAGCGAGGAACCTGTGCATGACCGTTAC

FIGURE 163

TGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTATAGGCTTTAAAATGTATATGT
CTTGCCATACTGAACCCATGTTGAAGCCATATTTCCACAGGGTAATAGCTGGCAGAACTGAGT
TAAGGGTTGCCCCTTTTAGATGAGGCATATGCTCTCCCATCCTCCACAGTTCACACTATGCNT
GCTTATCTCTTACTGATATTAGATATTAGTAATAGTCACATTTATGCATTGTCTTTATTTAAA
AAAATAGTTCTCTTTTTTATGACAGTAGCAATAGTTAGAATATGAAAGAGAGAAGAGGATTTA
TCCTTGCCCTACTCAATTCCTTGATATCATCTGCCTGGTAATGAGGTGTTGGAGCTGGCTAAT
ACTGACTTATGAGAGCATATTGTTAAATATTCAGGAATTTTACCAGCAGCAACCACCATTGGT
AGATTGGAATCAGCCACAGTGGGAGTATTTACACCAGGGAAATCAACGAACATTACAAATC

FIGURE 164

TTTCAAAAAAAAAAAAGTGCTTCTAGTAAATAACACATAACTTTTGTTTTATAACCCAATGTT
ACAGTCCCTCTCTTATAGGAGAACCCAATCCATTCAGTTTATCAGTGATATGCCTGTTTTTGT
GTGTTCCATCGGACTTTGTTTCCTTTTTTCGATTTTGTTATTGTTTCCACCTTTTCAATTTTC
TTACATTTGTTGGCTCTCTCAAGCTTCTGTTTATTCCCCTTCTCCCTCC

FIGURE 165

CCCGCTGCTCGGGCACTGTCTATATACGCCTAACACCTACATATATTTAAAAACATTAAATA
TAATTAACAATCAAAAGAAAGAGGAGAAAGGAAGGGAAGCATTACTGGGTTACTATGCACTTG
CGACTGATTTCTTGGCTTTTTATCATTTTGAACTTTATGGAATACATCGGCAGCCAAAACGCC
TCCCGGGGAAGGCGCCAGCGAAGAATGCATCCTAACGTTAGTCAAGGCTGCCAAGGAGGCTGT
GCAACATGCTCAGATTACAATGGATGTTTGTCATGTAAGCCCAGACTATTTTTTGCTCTGGAA
AGAATTGGCATGAAGCAGATTGGAGTATGTCTCTCTTCATGTCCAAGTGGATATTATGGAACT
CGATATCCAGATATAAATAAGTGTACAAAATGCAAAGCTGACTGTGATACCTGTTTCAACAAA
AATTTCTGCACAAAATGTAAAAGTGGATTTTACTTACACCTTGGAAAGTGCCTTGACAATTGC
CCAGAAGGGTTGGAAGCCAACAACCATACTATGGAGTGTGTCAGTATTGTGCACTGTGAGGTC
AGTGAATGGAATCCTTGGAGTCCATGCACGAAGAAGGGAAAAACATGTGGCTTCAAAAGAGGG
ACTGAAACACGGGTCCGAGAAATAATACAGCATCCTTCAGCAAAGGGTAACCTGTGTCCCCCA
ACAAATGAG

FIGURE 166

GGATTACAACCCCCGGGAGCGCGCCCTNTATACNTGGAACAACGGCCACCAGGTGCTATACAA
TGTCACCCTGTTTCACGTCATCAGCACCTNTGGGGGCCCTTTTCATTCGTGCCTGTGTCCCCN
CAAGGGTGATCTCTATGTNTATGTNACGCCCTTTNTCCCCGCCTTTTTGCTGGGCTTTTGTTC
TCTGCNTATGTATTTCTGTCTATTTTTTCAATTTCCCCTCTTCTCCTTTATTGATCTCTGCTT
TTAATACACCACTTCTTTCTTTCTGCCTTTTTATGGATGTCTTTTTCTTTTTATGGCTCTGGT
TCTCCAGTTCTTTCCGTCTCTGCCTCTCTCTGTCTCTCTCTCTCTGTCCT

FIGURE 167

TCAGCAAAACGTGGATTTAAATCTCNTTGCACAAGCTTGAGAGCAACACAATTTATCAGGAAA
GAAAGAAAGAAAAAAAACCGAACCTGACAAAAAAGAAGAAAAAGAAGAAGAAAAAAAAATCATGA
AAACCATCCAGCCAAAAATGCACAATTCTATCTCTTGGGCAATCTTCACGGGGCTGGCTGCTC
TGTGTCTCTTCCAAGGAGTGCCCGTGCGCAGCGGAGATGCCACCTTCCCCAAAGCTATGGACA
ACGTGACGGTCCGGCAGGGGGAGAGCGCCACCCTCAGGTGCACTATTGACAACCGGGTCACCC
GGGTGGCCTGGCTAAACCGCAGCACCATCCTCTATGCTGGGAATGACAAGTGGTGCCTGGATC
CTCGCGTGGTCCTTCTGAGCAACACCCAAACGCAGTACAGCATCGAGATCCAGAACGTGGATG
TGTATGACGAG

FIGURE 168

GGAGTGGCTTCCCCTACTGCGTGNTTTGACGCCCATCCCGGTGCTCACGTGGTTTTTCCCCCA
TCATCGGCCACATGGGCATCTGCACATCCACAGGAGTCATTCGGGANNTCGCGGGCCCNTACT
TTGTCTCNGAGGACAACATGGCCTTTGGAAAGCCTGCCAAGTACTGGAAGTTGGACCCTGCTC
AGGTCTATGCTAGCGGGCCCAACGCATGGGACACGGCTGTGCACGACGCCTCTGAGGAGTACA
AGCACCGCATGCACAATCTCTGNTGTGACAACTGCCACTCGCACGTGGCATTGGCCCTGAATC
TGATGCGCTACAACAACAGCACCAACTGGAATATGGTGACGCTCTGCTTCTTCTGCCTGCTCT
ACGGGAAGTACGTCAGCGTTGGGGCCTTCGTGAAGACCTGGCTGCCCTTCATCCTTCTCCTGGGC

FIGURE 169

TGGGAGATGTATGCTTACTCTCCTTAGCCTTTCATTCATCTTGGCAGGACTTANTGTTGGTGG
AGCCTGCATTTACAAGTACTTCATGCCCAAGAGCACCATTTACCGTGGAGAGATGTGCTTTTT
TGATTCTGAGGATCCTGCAAATTCCCTTCGTGGAGGNGAGCCTAACTTCCTGCCTGTGACTGA
GGAGGCTGACATTNGTGAGGATGACAACATTGCAATCATTGATGTGCCTGTCCCCAGTTTCTC
TGATAGTGACCCTGCAGCAATTATTCATGACTTTGAAAAGGGAATGACTGCTTACCTGGACTT
CCAG

FIGURE 170

GGAAGCAAAGGAGGAAGATCTACCACAGAAGGTTGAGGAAAAGTTCAACCTCACACAAGCACA
GATCAAACAGACAGCTTGGAATTNAGCAAACAACAGTTTTTACACCAGTAGCANGANTTCNTA
TTGTTAACTTTGATTATAGCATGGAGGAAAAGTTTGAATCCTTTTCAAGTTTTCCTGGAGTAG
AATCAAGTTATAATGTGTTACCAGGAAAGAAGGGACACTGTTTGGTAAAGGGCATAACCATGT
ACAACAAAGCTGTGTGGTCGCCTGAGCCCTGCACTACCTGCCTCTGCTCAGATGGAAGAGTTC
TTTGTGATGAAACCATGTGCCATCCCCAGAGGTGCCCCCAAACAGTTATACCTGAAGGGGAAT
GCTGC

FIGURE 171

ACTACATTGCCTGGAGGAAGCCTAAGGAACCCAGGCATCCAGCTGCCCACGCCTGAGTCCAAG
ATTCTTCCCAGGAACACAAACGTAGGAGACCCACGCTCCTGGAAGCACCAGCCTTTATCTCTT
CACCTTCAAGTCCCCTTTCTCAAGAATCCTCTGTTCTTTGCCCTCTAAAGTCTTGGTACATCT
AGGACCCAGGCATCTTGCTTTCCAGCCACAAAGAGACAGATGAAGATGCAGAAAGGAAATGTT
CTCCTTATGTTTGGTCTACTATTGCATTTAGAAGCTGCAACAAATTCCAATGAGACTAGCACC
TCTGCCAACACTGGATCCAGTGTGATCTCCAGTGGAGCCAGCACAGCCACCAACTCTGGGTCC
AGTGTGACCTCCAGTGGGGTCAGCACAGCCACCATCTCAGGGTCCAGCGTGACCTCCAATGGG
GTCAGCATAGTCACCAACTCTGAGTTCCATACAACATCCAGTGGGATCAGCACAGCCACCAAC
TCTGAGTTCAGCACAGCGTCCAGTGGGATCAGCATAGCCACCAACTCTGAGTCCAGCACAACC
TCCAGTGGGGCCAGCACAGCCACCAACTCTGAGTCCAGCACACCCTCCAGTGGGGCCAGCACA
GCCACC

FIGURE 172

TACATTGCCTTGGAGGAAGCNTAAGGAACCCAGGCATCCCAGCTGCCCACGCCTGAGTCCAAG
ATTCTTCCCAGGAACACAAACGTAGGAGACCCACGNTCTTGGAAGCACCAGCCTTTATCTCTT
CACCTTCAAGTCCCCTTTCTCAAGAATCCTCTGTTNTTTGCCCTCTAAAGTCTTGGTACATCT
AGGACCCAGGCATCTTGCTTTCCAGCCACAAAGAGACAGATGAAGATGCAGAAAGGAAATGTT
CTCCTTATGTTTGGTCTACTATTGCATTTAGAAGCTGCAACAAATTCCAATGAGACTAGCACC
TCTGCCAACACTGGATCCAGTGTGATCTCCAGTGGAGCCAGCACAGCCACCAACTCTGGGTCC
AGTGTGACCTCCAGTGGGGTCAGCACAGCCACCATCTCAGGGTCCAGCGTGACCTCCAATGGG
GTCAGCATAGTCACCAACTCTGAGTTCCATACAACCTCC

FIGURE 173

GACAAAGGNTCATTTGTAAAGAAGCTCCTTCCAGCACCTCCTNTCTTCTCNTTNTGCCCAAAC
TCACCCAGTGAGTGTGAGCATTTTAAGAAGCATCCTCTGCCCAAGACCAAAAGGAANGAAGAA
AAAGGGCCAAAAGCCAAAATGAAACTGATGGTACTTGTTTTCACCATTGGGCTAACTTTGCTG
CTAGGAGTTCAAGCCATGCCTGCAAATCGCCTCTCTTGCTACAGAAAGATACTAAAAGATCAC
AACTGTCACAACCTTCCGGAAGGAGTAGCTGACCTGACACAGATTGATGTCAATGTCCAGGAT
CATTTCTGGGATGGGAAGGGATGTGAGATGATCTGTTACTGCAACTTCAGCGAATTGCTCTGC
TGCCCAAAAAAC

FIGURE 174

GTTTGGTAAGACTCCAGACTCCAGCTAACAGTCCCTATGGAAAGATGGCATCAAAAAAGATAG
ATCTATATATATATATATAAATATATATTCTATTACATTTTCAGTGAGTAATTTTGGATTTTGCA
AGGTGCATTTTTACTATTGTTACATTATGTGGAAAACTTATGCTGATTTATTTAAGGGGGAAA
AAGTGTCAACTCTTTGTTATTTGAAAACATGTTTATTTTTCTTGTCTTTATTTTAACCTTTGA
TAGAACCATTGCAATATGGGGGCCTTTTGGGAACGGACTGGTATGTAAAAGAAAATCCATTAT
CGAGCAGCATTTTATTTACCCCTCCCCTATCCCTAGGCACTTAACCAAGACAAAAAGCCACAA
TGAACATCCCTTTTTCAATGAATTTTATAATCTGCAGCTCTATTCCGAGCCCTTAGCACCCAT
TCCGACCGAG

FIGURE 175

CGGATTGGATGGATTGNTTGAACGGATTGGGTTGGGGGAAGNAAAGGGAAAGGAGGGAGAAAG
GAGGGAATAACTGGGCTCCATCTTTTGAGAGCTNTTGGTTGGGCAAGGGCAGAAAACAGGCCC
ACAGTGCTCAACCCCGGACACCCTCACGAAGGTTCGCAAAGTCACTNCTTGTGGCTTCAGATT
GCTCTTTAGGACCTGGAGGGACAGACCCAGAATCAGGGTCCCCTCCTTTACCCCCTGAGTTCC
TTACTGTTCCCCCAAGCCTGGGAGCAGTCTATCCCCCAACCCTGCCATCTCCCTTACTCATCC
CTCTTCCACAGCTTCCCCTTTCTAGCCCCCTCTGCCCTACCTGTCTTTCCTGAGTGTTTGAGG
GGAGAGAGAGACCCACATCTCCCCAAAGAGATGAGCTTTTGGGGCACAACATCCCACCGCAGG
CCCCCTCACCCGACAACACCTCCTACCTGGCCCCTTGCCAAATCCCAAGCAGAATTAGCAACA
GGAAAAGCAGAGCCCCAGGAGAGACACTCTACTATATATACTCTTCTATATATTCTGTTTCTA
TTGTATATTCACTCTGTACATGTGGGTGTAAATGCTGTTAAATGACAAACCCAATATTATACT
GTGGCTGGTGGACTATTTTCATCCTCAGTGCTGTACAGATCTATTTTCATTGTATATTTGAT

FIGURE 176

TGGATGGGCGGCCAGCGATGACCCCATTGAGAAGGTCATTGAAGGGATCAACCGAGGGNTGAG
CAATGCAGAGAGAGAGAGGTGGGCAAGGCCCTGGATGGCATCAACAGTGGAATCACGCATGCCGG
AAGGGAAGTGGAGAAGGTTTTCAACGGACTTAGCAACATGGGGAGCCACACCGGCAAGGAGTT
GGACAAAGGCGTCCAGGGGCTCAACCACGGCATGGACAAGGTTGCCCATGAGATCAACCATGG
TATTGGACAAGCAGGAAAGGAAGCAGAGAAGCTTGGCCATGGGGTCAACAACGCTGCTGGACA
GGGCAACCATCAAAGCGGATTTTCCAGCCATCAAGGAGGGGCC

FIGURE 177

GACCTTCCCAGCAATATGCATCTTGCACGTCTGGTCGGCTCCTGCTCCNTCCTTCTGNTACTG
GGGGCCCTGTNTGGATGGGCGGCCAGCGATGACCCCATTGAGAAGGTCATTGAAGGGATCAAC
CGAGGGCTGAGCAATGCAGAGAGAGAGGTGGGCAAGGCCCTGGATGGCATCAACAGTGGAATC
ACGCATGCCGGAAGGGAAGTGGAGAAGGTTTTCAACGGACTTAGCAACATGGGGAGCCACACC
GGCAAGGAGTTGGACAAAGGCGTCCAGGGGNTCAACCACGGCATGGACAAGGTTGCCCATGAG
ATCAACCATGGTATTGGACAAGCAGGAAAGGAAGCAGAGAAGCTTGGCCATGGGGTCAACAAC
GCTGCTGGACAGGTTGGGAAGGAGGCAGACAAACTGATCCATCATGGGGTCCATCACGGGGCC
AACCAGGCG

FIGURE 178

ATTGAATNACAGTTTTTCTGGTTTTTTTGTGGAGTTTTTGTTTTGGTTTTTGAGATGGAGTTT
NGNTNTTGTTCCCCAGGCTGGAGTGTGGTGGTGCGATTTCGGCTTACCGCAACTTCTGCTTCC
CGGGTTCAGGCAGTTTTCCTGCNTCGGCTTCCTGAGTGGCTGGTATTACGGGCATGCACCGTC
GCGCCCCACTGGTTTTGTATTTTTTTAGTAGAGACGGGGTTTTTCCGTGTTGGTCAGGCTGGT
CTCGAACTCCCGACCTCAGGTGATCCGCCCGCCTCGGCCTCCCAAGGTTNTGGGATTGCAGGT
GTGAGCCACCGTGCCCGGCTGTTTTTTGTGGGTTTTTTGTTTGTTTGTTTGTTTTTGAGACAG
AGTCTTGCTCTGTCACTCAGGCTGGAGTGCAGTGGCACAGTCTCGGCTCACTGCAACCTCTGC
CTCCTGAGTTCAAGCCATTNTCCTGCCTCGGCCCCCTCAGTAGCTGGG

FIGURE 179

GGGCGAGAAGTAGGGGAGGGCGTGTTCCGCCGCGGTGGCGGTTGCTATCGTTTTGCAGAACCT
ACTCAGGCAGCCAGNTGAGAAGAGTTGAGGGAAAGTGCTGCTGCTGGGTCTGCAGACGCGATG
GATAACGTGCAGCCGAAAATAAAACATCGCCCCTTCTGCTTCAGTGTGAAAGGCCACGTGAAG
ATGCTGCGGCTGGCACTAACTGNGACATCTATGACCTTTTTTATNATCGCACAAGCCCCTGAA
CCATATATTGTTATCACTGGATTTGAAGTCACCGTTATCTTATTTTTCATACTTTTATATGTA
CTCAGACTTGATCGATTAATGAAGTGGTTATTTTGGCCTTTGCTTGATATTATCAACTCACTG
GTAACAACAGTATTCATGCTCATCGTATCTGTGTTGGCACTGATACCAGAAACCACAACATTG
ACAGTTGGTGGAGGGGTGTTTGCACTTGTGACAGCAGTATGCTGTNTTGCCGAC

FIGURE 180

GGGAGGCTGTGNCCGTTTTGTTTTNTTGGCTAAAATCGGGGGAGTGAGGCGGCCCGGCGCGGC
GNGACACCGGGTTCCGGGAACCATTGCACGACGGGGTGGACTGACCTGAAAAAAATGTTTGGA
TTTNTAGAGGGCTTGAGATGCTCAGAATGCATTGACTGGGGGGAAAAGCGCAATACTATTGCT
TCCATTGCTGCTGGTGTACTATTTTTTACAGGCTGGTGGATTATCATAGATGCAGCTGTTATT
TATCCCACCATGAAAGATTTCAACCACTCATACCATGCCTGTGGTGTTATAGCAACCATAGCC
TTCCTAATGATTAATGCAGTATCGAATGGACAAGTCCGAGGTGATAGTTACAGTGAAGGTTGT
CTGGGTCAAACAGGTGCTCGCATTTGGCTTTTCGTTGGTTTCATGTTGGCCTTTGGATNTCTG
ATTGCATCTATGTGGATTCTTTTTGGAGGTTATGTTGCTAAAGAAAAAGACATAGTATACCCT
GGAATTGCTGTATTTTTCCAGAATGCCTTCATNTTTTTGGAGGGCTG

FIGURE 181

TTCTTTTTAGAGATTCCNTTGGACCTTGACCCAAGGTTTCCGACAGGTTTTTTTTGAATTTT
GGAACAGACCTTTATATTTTGGGNCNAGAAGTTNGCCCAGAAAGCAGCAGGGGTTTTGCCTGG
NTGTAGAGCCCAGTTCATTGGNTGTCCCTGGGTTTGTTTCCTTNTTCCGAGTAGTTGTGCCTT
TTTTCAGATCAGGTTACCACAATGCTCCCCGNTGTGACGTTTNATCCCCCACACTTCCAGCCC
CAGTTACCTGGAGTTTTTCAGAACCCACTTTGCCGGTGTTAAAACACAAGAGGGGGTGAAAGT
GGCTGCCAGTAATGGCCAGAAACCAACCACCAGAGGCCAGGNTGAAAGACAAGTTCCGGGTGT
CCAGGGGCTGACGGGCCAACCATGTGGCAGGTCCCAGGCCCCACCCANTGCGCCATCCGCTTC
TGAGCTCCACAGTGGTCCCACTAATGGGAACCTCCTNTAGGGAGAGTGATACTGCACCTTCAC
CCGTAGGACTCATATTTATAACAATGTGTAATGGCTGTAGCAAAAAGCCCTTGTTTNTAGATG
TAAATGGTCAAAGAAACAAGCGTTTTATTGTTTTGAATAAAATAGTTCAAATGAGTCCTGTAT
CATTGTATCTCCTATTCTGGATTAGTGCCTTTTGGACAGTAGACTGTTCTGTAATTAAAA

FIGURE 182

AATTTTCACCGCTGTAGGAATCCAGATGCAGGCCAAGTACAGCAGCACGAGGGACATGNTGGA
TGATGATGGGACACCACCATGAGCCTGCATTNTCAAGCTTTTGCCACAATTCGGCATCCAGAG
CCCCGGCGCACAGAGCACAGGGNTCCTTTTTCAACGTGGCGACCAGTGGCCCTGACCCTGCTG
ACTTTGTGCTTGGTGCTGCTGATAGGGCTGGCAGCCCTGGGGCTTTTGTTTTTTCAGTACTAC
CAGCTCTCCAATACTGGTCAAGACACCATTTCTCAAATGGAAGAAAGATTAGGAAATACGTCC
CAAGAGTTGCAATTTNTTCAAGTCCAGAATATAAAGCTTGCAGGAAGTNTGCAGCATGTGGCT
GAAAAACTCTGTCGTGAGCTGTATAACAAAGCTGGAGGAACTTTGAAGGAGGGCAAAGTNTCC
TCATNTACTATACACACACCACTTCCC

FIGURE 183

TCACAGCATGAGAGAGATCCNTGGTATAGCTGGGACCAGCCGGGCCTGANGTTGAACTGGGGT
GAACCGATGCACTGGCACCTNGACATNTACAACAGGAACCGTGTGGANACATCCCCCACACCT
GTTTNTTGGCATGTCATGTGTATGCAGNTCTTCGGTTTCCTGGCTTTNNTGATATTCATGTGN
TGGGTGGGGGANGTGTACCCTGTCTACCAGCCTGTGGG

FIGURE 184

GAAAGAAGGAAATAAACACAGGCACCAAACCANTATCCTAAGTTGACTGTCCTTTAAATATGT
CAAGATCCAGACTTTTCAGTGTCACCTCAGCGATCTCAACGNTAGGGATCTTGTGTTTGCCGN
TATTCCAGTTGGTGCTCTCGGACCTACCATGCGAAGAAGATGAAATGTGTGTAAATTNTAATG
ACCAACACCNTAATGGNTGGTATATCTGNATCCTCCTGCTGCTGGTNTTGGTGGCAGCTCTTC
TCTGTGGAGCTGTGGTCCTCTGCCTCCAGTGCTGGCTGAGGAGACCCCGAATTGATTCTCACA
GGCGCACCATGGCAGTTTTTGCTGTTGGAGACTTGGACTCTATTTATGGGACAGAAGCAGCTG
TGAGTCCAACTGTTGGAATTCACCTTCAAACTCAAACCCCTGACCTATATCCTGTTCCTGCTC
CATGTTTTGGCCCTTTAGGCTCCCCTCCTCCCT

FIGURE 185

CCGAAACGCGGTCTTTCTCTAGACGCGTCTTGCTGGGAGAGTGTCCGTTGCTTCCCGTCCGTG
TCGCGGCCCTGCGGTTGGCGGCCTCCTCGTGGAGCGGAGCAAGGCTGAGATCTGTATCTGTGG
ACCTGAATGTTGATCCCTCGCTTCAGATTGACATACCTGATGCGCTCAGTGAGAGAGACAAAG
TCAAATTTACAGTGCACACAAAGACCACACTGCCCACGTTTCAGAGCCCAGAGTTTTCTGTTA
CAAGGCAACATGAAGACTTTGTGTGGCTACATGACACTCTTATTGAAACAACAGACTATGCTG
GGCTTATTATTCCACCTGCTCTTTG

FIGURE 186

GGCTGGAGCAAATGCTCCACAGCTGCCGAATCCAGAAGTCAGATTTCAGCAACAACTGGAACA
GCTCAACGCAATGGGGTTCTTAAACCGTGAAGCAAACTTGCAGGCCCTAATAGCAACAGGAGG
CGACATCAATGCAGCCATTGAAAGGCTGCTGGGCTCCCAGCCATCGTAATCACATTTCTGTAC
CTGGAAAAAAATGTATCTTATTTTTGATAATGGCTCTTAAATCTTTAAACACACACACAAAAT
CGTTCTTTACTTTCATTTTGATTCTTTTAAATCTGTCTAGTTGTAAGTCTAATATGATGCATT
TTAAGATGGAGTCCCTCCCTCCTACTTCCCTCACTCCCTTTCTCCTTTGCTTATTTTTCCTAC
CTTCCCTTCCTCTTGTCTCCCCACTCCCCTCCC

FIGURE 187

CTTAGCATAAACCTACAGGGCCCTGTGTGATCGGACTCCTGCCCACTTGACATGTTAGTTACT
TGCCCCTCGTTGCTTCGTGCTTTACCTTCCAGAATCATTAAACTGCTGATGTTTCCCAAAAAT
AACTATGTACCTGGGTCAGCTCATGCTGGCATGGAGTTCTCGTCCATCACCATGCCCACCCTG
GCTTCTTTGAGCGCCCGTATAATATATATCTCTACCATCATACTTCATATATTTTGTTATAAT
TGCTGGTTTTATTTGCCTCTGTGGT

FIGURE 188

AAAAATCCTGGTTTTTTTTGGGTTTTTTTTTGCTGTGCCCTAGACCATTACATAACTGAAGA
CTCCCACCTTCAGGCAGGTTTGGGTAGTACACGTTTGTAACTACCTGGCATTGCCTTTTGTTG
AAGTAATTTCAGTTTTTATTAGTAGTAGTAGTAGTATACTTTGGGTTCTACAGTATATGTTCA
CAATGTGCAGGTTTGTTACATATGTATACATGTGCCATGTTTGTTTGCTGCACCCATTAACTG
GTCATTTACATTGGGTATTTCTCCTAATACTATCCCCCCCGC

FIGURE 189

GTAACATTTGGGAGTGACAAGACTGTTCATCAGCTTGGGGCCTGGCAGCAACTTTTCTAGAGT
TAGCTTTTTTCTCCTTTCTTGTTCCATGACTTAAAAATAATAACTTGTTGGGCATGGTGCCTC
ATTCTTGTAATCCCAGCACTTTGGGAGGCTGAGGCACTTGTGGCCAGGAGTTCAAGACTAGCC
TGGGCAACGTAGTAGATGCCCTCCCCGCCACCATCTCTACAAAAGAAAAAAAGTTAACTCTTG
ATTTGCTTTCTAGTAGTGGGTGAATTTGGAGTTCCAATGATTGTCAACCCATTAATTCTTCAT
TTACTGAACATCTCCTTATGTTTCAGATGCTGCAAAGATGTACAAGACTTTGTTTCCTACCCT
CCTTTTT

FIGURE 190

TGCAATCTGCCTTGTGTGCTGTTGTAAACAAGTTAGTGTTCAACCAGTGTTTAAAGTGTCTGT
TTTAAAAGCTCTAATTATGGTAGTATTTCCATTTCCTTTTACAACACCCTTTATTTTGTTCCT
CCAGGTTC

FIGURE 191

TTTTAAAAAAAAAAAAAAACAAAGAAATTCTATGTTAACTCAATACCAACATCTTGCAGAACT
AGAGTACAATATCACAGCCAGGATGTTGACCTTGATACGAGCCATCAGTCTTATTCGGGTTTT
CCCAAATTTACTTTGTGTGTGTGTGTGTCTGTGTGTAGTTAGGTCTATGCTAGTTTATGACGT
GCAGTTTCATGTATCTCCCACCACAGCCAACACACAGAACAGTTCCATCTCCCCTC

FIGURE 192

GGTTTCGCCATGTTGCCCAAGCTGTTCTTGAACTCCCGGGCTCAGGTGATCCGCCTCCCTCGG
CCTCCCAGAGTGCTGGGATTACAGGCACGGACCACCATGCCCAGCCTCCACATCTTTTTTTGC
ACTGTGTATACTCTTCTGAGACATGCCAACTTCCTCCAGGTCAAGAAAGGGGTATATAGCTCT
CAGCTTCACTCTTTCAGGGCTGATGTCGCCTTTGCCTTTTCTCACTTCACTGACCTGTCTATT
CCTACAACTGTCTCTTTCTAGAGAAGCCTCAATGATCAGGATTGACAGGCCACACTCTCCCCC
ACCTTTCT

FIGURE 193

CAGCATGAGCTCCCTGTGTGTGCAAGGCAGCTCTATGCGGTTCTCGGTGTCTCCTAGGAAGCA
ACTTTCAGTACCCTCCTGTGTTGAGTCCGATTTTCTAAAAGCTGAGCGGGCATCTAGGGACCT
TTCTGTCACTCAGCCGACTGTGTGGCTGTGGCCAGCTCTGGGTCTGCCTCCCCCAGAACTAGA
TGCCCATGGGGAGTCCATCAGCACCAATCTCCTGTGATCGTTTATACAACAGAATCTCCACTC
AAGTAAAAGTGGGGCCTCCTCCTATCTTGCTGTTTGTGTGTGTGTTGGCAGACCCCAGCGTGG
CTGGAACAGATGATTGCACATACCACGTGGCGGGACCTTTTTTATAAACTGGCTGAAGCCCAT
CCAGACTGTTTGATGCTGAACTTCACCGTTAAGGTAGGAAGAGTTCTAGAGTTAAGGAGAAAA
GTGTTTATGAATGTTTATTTTTGGTTGTTGGTCTGTTTGG

FIGURE 194

ATAGCTCTCAGCTTCACTCTTTCAGGGCTGATGTCGCCTTTGCCTTTTCTCACTTCACTGACC
TGTCTATTCCTACAACTGTCTCTTTCTAGAGAAGCCTCAATGATCAGGATTGACAGGCCACAC
TNTCCCCCACCATTTTTTTCTCCTCCTTCAAGCCTCTTGTCTGTTTCACCCTCTAGTG

FIGURE 195

GTTTAATTATGGTATGCAACCACTCATGTATTCGGTTCAGGAAGCATTAAATGCCAGACCATG
GTGGATTCGTATGGGGACTGACATTTGTTACTATAAAAATCATTTCTCAAGAAGTTCAGTTGC
TGCAGGTGGGCAAAAGGGAAAATCCTACTATACAATTACATTTACTGTCAATTTTCCACATAA
AGATGATGTTTGCTACTTTGCTTATCACTATCCTTT

FIGURE 196

CTGACATTCATTGTGATGAGGGCAGCTTTCTGGTACAGGATTCTAAGCTCTATGTTTTATATA
CATTTTCATCTGTACTTGCACCTCACTTTACACAAGAGGAAACTATGCAAAGTTAGCTGGATC
GCTCAAGGTCACTTAGGTAAGTTGGCAAGTCCATGCTTCCCACTCAGCTCCTCAGGTCAGCAA
GTCTACTTCTCTGCTATAG

FIGURE 197

ATCTTGGCCGTATGAAAGTATAACACTAAGAAAAAAATTCATTTTTTTCAAACGTAACCTTCC
ATTCTTTCTCCCTTTTCCTCTAAACTAAAACCTTCTTTCCCATCTTTTNTTTCTTGAACCAGA
CTAATCTAGACAAAGATCTCAGCCTCTGCCAGACAGAGTTAGAGGCAGATTTAGAAAAAATGG
AGACGCTTAATAAAGCACCCAGTGCAAACGTGCCACAGGTATTTCCTAGTTTTTCTCATGCCA
TCAGTTCCTTTTCAAGCTGTGCTTTGTTTTCTTCTTTGTTCTATGGTTTTTGATGTAGTTGAG
GTGACGGATGGTGATGCTGGCTATTTTAGGCTGCATGGCTTTCTGACTACTGTTTTAGACTCC
TTCCCCCACACCTACCCAGTTAGTA

FIGURE 198

GTTGAACGCCACCGAGGGTCAAGTCACAGACAAGAAGCTGTGCAGTCACCAGTGTTTCCTCNT
GCCCAGAAACAAATCCACCAAAAACCCATACCTCTGCCAAGATTTACAGAAGGGGGAAACCCA
ACTGTGGATGGGCCCCTACCCAGNTTTTCATNTAATTCCACTATTTCAGAACAGGAAGCTGGC
GTTCTNTGCAAGCCATGGTATGCTGGAGCCTGTGATCGAAAGTCTGNTGAAGAGGCATTGCAC
AGATCAAACAAGGATGGATCATTTCTTATTCGGAAAAGCTCTGGCCATGATTCCAAACAACCA
TATACACTAGTTGTATTCTTTAATAAGCGAGTATATAATATTCCTGTGCGATTTATTGAAGCA
ACAAAACAATATGCCTTGGGCAGAAAGAAAAATGGTGAAGAGTACTTTGGAAGTGTTGCTGAA
ATCATCAGGAATCATCAACATAGTCCTTTGGTTCTTATTGACA

FIGURE 199

GGCGGCTGGGCTGTTTGGTTTGAGCGCTCGCCGTCTTTTGGCGGCAGCGGCGACGCGAGGGCT
CCCGGCCGCCCGCGTCCGCTGGGAATCTAGCTTCTCCAGGACTGTGGTCGCCCCGTCCGCTGT
GGCGGGAAAGCGGCCCCCAGAACCGACCACACCGTGGCAAGAGGACCCAGAACCCGAGGACGA
AAACTTGTATGAGAAGAACCCAGACTCCCATGGTTATGACAAGGACCCCGTTTTGGACGTCTG
GAACATGCGACTTGTCTTCTTCTTTGGCGTCTCCATCATCCTGGTCCTTGGCAGCACCTTTGT
GGCCTATCTGCCTGACTACAGGATGAAAGAGTGGTCCCGCCGCGAAGCTGAGAGGCTTGTGAA
ATACCGAGAGGCCAATGGCCTTCCCATCATGGAATCCAACTGCTTCGACCCCAGCAAGATCCAG

FIGURE 200

GGTCCGAAAAGTAAGTTCTTNTTTTGGGCTNAACGGGATTTCCTTNTTTGCAGTTTTGCAGCC
CCAGNACGNTGATTCCCAGCAGGCGCTTTACNGGGCAGCCCGAAGATTTCACTTATGGTGAAA
ATCGCCTTTCAATACCCTTACCGCCGTGCAAAAGGAGGAGGCGCGGCAAGACTTGGAGGCCCT
TCTTGACCCGAACGGTCAGAACTCAGGATANTGACCGGCAAGGAGCTCCGAGTTGCCACCCAG
GAAAAAGAGGGCTCCTCTGGGAGATGTATGCTTACTCTCTTAGGCCTTTCATTCATCTTGGCA
GGACTTATTGTTGGTGGAGCCTGCATTTACAAGTACTTCATGCCCAAGAGCACCATTTACCGT
GGAGAGATGTGCTTTTTTGATTCTGAGGATCCTGCAAATTCCCTTCGTGGAGGAGAGCCTAAC
TTCCTGCCTGTGACTGAGGAGGCTGACATTCGTGAGGATGACAACATTGCAATCATTGATGTG
CCTGTCCCCAGTTTCTCTGATAGTGACCCTGCAGCAATTATTCATGACTTTGAAAAGGGAATG
ACTGCTTACCTGGACTTGTTGCTGGGGAACTGCTATCTGATGCCCCTCAATACTTCTATTGTT
ATGCCTCAAAAAAATCTGGTAGAGCTCTTTGGCAAACTGGCGAGTGGCAGATATCTGCCTCAA
ACTTATGTGGTTCGAGAAGACCTAGTTGCTGTGGAGGAAATTCGTGATGTTAGTAACCTTGGC

FIGURE 201

GATGGGTTTCCAAGCGTTCATTCAAAAACTTGCTGGGTAATCCCCAGGCCTCTATAGCTCAGA
TCATTGTCACAGTCGTACTGGGACTGGTTATAGGTGCCATTTACTTTGGGCTAAAAAATGATT
CTACTGGAATCCAGAACAGAGCTGGGGTTCTCTTCTTCCTGACGACCAACCAGTGTTTCAGCA
GTGTTTCAGCCGTGGAACTCTTTGTGGTAGAGAAGAAGCTCTTCATACATGAATACATCAGCG
GATACTACAGAGTGTCATCTTATTTCCTTGGAAAACTGTTATCTGATTTATTACCCATGAGGA
TGTTACCAAGTATTATATTTACCTGTATAGTGTACTTCATGTTAGGATTGAAGCCAAAGGCAG
ATGCCTTCTTCGTTATGATGTTTACCCTTATGATGGTGGCTTATTCAGCCAGTTCCATGGCAC
TGGC

FIGURE 202

GCGGCCCCCTTGGGGTTTGGATTCAGGATTTGTTCCTAGTGTCCAAGATTTTGTTAGGAACTT
ACNGAAGTTGATGCTTACCTACAAATCTTGATTGAACAATTAAAGCTTTTTGATGACAAGCTT
CAAAACTGCAAAGAAGATGAACAGAGAAAGAAAATTGAACTNTCAAAGAGACAACAAATAGCA
TGGTAGAATCAATTAAACACTGCATTGTGTTGCTGCAGATTGCCAAAGACCAGAGTAATGCGG
AGAAGCACGCAGATGGAATGATAAGTACTATTAATCCCGTAGATGCAATATATCAACCTGGTC
CTTTGGAACCTGTGATCAGCACAATGCCTTCCCAGACTGTGTTACCTCCAGAACCTGTTCAGT
TGTGTAAGTCAGAGCAGCGTCCATCTTCCCTACCAGTTGGACCTGTGTTGGCTACCTTGGGAC
ATCATCAGACTCCTACACCAAATAGTACAGGCAGTGGCCATTCACCACCGAGTAGCAGTCTCA
CTTCTCCAAGCCACGTGAACTTGTCTCCAAATACAGTCCCAGAGTTCTCTTACTCCAGCAGTG
AAGATGAGTTTTATGATGCTGATGAATTCCATCAAAGTGGCTCATCCCCAAAGCGCTTAATAG
ATTCTTCTGGATCTGCCTCAGTCCTGACACACAGCAGCTCGGGAAATAGTCTAAAACGCCCAG
ATACCAC

FIGURE 203

CATGCAGTGCTTCAGCTTCATTAAGACCATGATGATCCTCTTCAATTTGCTCATCTTTCTGTG
TGGTGCAGCCCTGTTGGCAGTGGGCATCTGGGTGTCAATCGATGGGGCATCCTTTCTGAAGAT
CTTCGGGCCACTGTCGTCCAGTGCCATGCAGTTTGTCAACGTGGGCTACTTCCTCATCGCAGC
CGGCGTTGTGGTCTTTGCTCTTGGTTTCCTGGGCTGCTATGGTGCTAAGACTGAGAGCAAGTG
TGCCCTCGTGACGTTCTTCTTCATCCTCCTCCTCATCTTCATTGCTGAGGTTGCAGCTGCTGT
GGTCGCCTTGGTGTACACCACAATGGCTGAGCACTTCCTGACGTTGCTGGTAGTGCCTGCCAT
CAAGAAAGATTATGGTTCCCAGGAAGACTTCACTCAAGTGTGGAACACCACCATGAAAGGGCT
CAAGTGCTGTGGCTTCACCAACTATACGGATTTTGAGGACTCACCCTACTTCAAAGAGAACAG
TGCCTTTCC

FIGURE 204

GAATCGATAGAACCGAGGTGCAGTTGGACCTGGGAGTGGACACCAAGATTTTAAAAGCTCCAA
TTTCAGAGCAAGAGTCGAAAACTCACAGATAAAGTTATAGTTATTTCAGGGTTCTGAAAAGAC
GCAGAACATGAAGGGACTCAGAAGTCTGGCAGCAACAACCTTGGCTCTTTTCCTGGTGTTTGT
TTTCCTGGGAAACTCCAGCTGCGCTCCGCAGAGACTGTTGGAGAGAAGGAACTGGACTCCTCA
AGCTATGCTCTACCTGAAAGGGGCACAGGGTCGCCGCTTCATCTCCGACCAGAGCCGGAGAAA
GGACCTCTCCGACCGGCCACTGCCGGAAAGACG

FIGURE 205

TCCAGGAGACGACTAAAATGGGCTGTCTTCATCGGTGGAATACAACATAATGGAGTTGGAACA
AGAACTTGAAAATGTAAAGACTCTTAAGACAAAATTAGAGAGGCGAAAAAAGGCTTCAGCATG
GGAAAGAAATTTGGTGTATCCCGCTGTTATGGTTCTCCTTCTTATTGAGACATCCATCTCGGT
CCTCTTGGTGGCNTGTAATATTCTTTGCCTATTGGTTGATGAAACAGCAAATGCCAAAAGGAA
CAAGGGGGCCTGGAATAGGAAATGCCTCTCTTTCTACGTTTGGTTTTGTGGGAGCTGCGCTTG
AAATCATTTTGATTTTCTATCTTATGGTGTCCTCTGTTGTCGGCTTCTATAGCCTTCGATTTT
TTGGAAACTTTACTCCCAAGAAAGATGACACAACTATGACAAAGATCATTGGAAATTGTGTGT
CCATCTTGGTTTTGAGCTCTGCTCTGCCTGTGATGTCGAGAACACTGGGAAT

FIGURE 206

CTATTAGAGATTCCCCTTGGACCCTTGGACCCAACGGNGTCCCGGGGNACACCCCCTTTTTTC
AGAAACCCAGGGCTGTGTAAGAGCTGCTTGGAGTAGGCACCCCATTTAAAGAAAAAAATGAAG
AAGCAGCAATAAAGAAGTTGTAATCGTTACCTAGACAAACAGAGAACTGGTTTTGACAGTGTT
TNTAGAGTGCTTTTTATTATTTTCCTGACAGTTGTGTTCCACCATGATTACTTTCTCCTTCAG
CGAATAGGNTAAATGAATATGAAACAGAAAAGCGTGTATCAGCAAACCAAAGCACTTCTGTGC
AAGAATTTTCTTAAGAAATGGAGGATGAAAAGAGAGAGCTTATTGGAATGGGGCCTCTCAATA
CTTCTAGGACTGTGTATTGCTCTGTTTTCCAGTTCCATGAGAAATGTCCAGTTTCCTGGAATG
GCTCCTCAGAATCTGGGAAGGGTAGATAAATTTAATAGCTCTTCTTTAATGGTTGTGTATACA
CCAATATCTAATTTAACCCAGCAGATAATGAATAAAACAGCACTTGCTCCTCTTTTGAAAGGA
ACAAGTGTCATTGGGGCACCAAATAAAACACA

FIGURE 207

TGCCTTTTCCTCTGACCCTTCAGGTCCCTCACCGAGTTTTGCTCCAGGNGTATATTGAAAACA
TACCCAGTGCTNTNTCAAGCACCCACTGCTTAGAGGGCCCAGATTTCTTTTCCTTCTTTCCCT
TGCAGAGCTGGAGACTGCATCGGGCATCTGGTGTTTAAACTAAACAGGAAAACTGACTAAAGG
TCCACAGTGCTCATTGTGTAGACTAGCTGCCCTCCGATGGGTGCTCTGATTATCAGTGGTTCC
AGTGCAGGGCCTGTCACTAAACAGGCCTCANTTCCTCCTTGGGGGCTTTCCCATGGGAGGTGT
GGCTTTTTACTCTACATGGAAATGACTCTCTGCAGCCACAGAACACAGTCATTTTCTGAATTA
TCCCAGTCTCTCATGCGCCCTGGATTCCTCCAGATGCCTTATATCTCTTGTGCAAAGTTGTCT
AAAATTTGGTTCCCAGNTTCCAAGCCTTGCCTTTTGGCCTTCCTGGAAGTATTTTTGTTGATG
AGTCGTCTGTCATTATTCTCTAAAATGATTTGCTTTTTGTTTCTTTCATTCCTATTTCCACCC
CACATATACAC

FIGURE 208

TCTTTCTGTAAGACTCAACTGATATATATTATACTGATGCAAATATTAAGTAGGGCATAAAAA
TATGCTTCCATAATATGAAATAGATTATTCAATAATTGAGAAACTTTATGTGTAATCATGAGA
GTATAAGAGTCTGGATTATCTAACATTGTTAGCCCTGTGTATGTACAGTTCAAAAAGTTCATT
TATAAAAGTAGTTTCCTGTTCCTAGTGTGATGTATCACAAATTGTGCTGAGGTTATTTTAGTA
TGTGTGTTTCATTCCCGTGCTTCTGTTCTGAAGTCCTGGAATACAGTTTTCAGTGTAATTAAT
TCAACTGCACTTAACANTAATGTCCGTGTTGGTATAGAAATGTCTAAATCCTATACTCTAGTT
GAGGAAGATCTTCCATAATTTTATGGTATTACACAGGGAAAGCTATGANTGCAGGATCAGTCT
AANTATANTATTAGGTGCATGTATTCTCTTTTCACTAANTTATACTTGTCTATCTAGAATACA
GGTNTTCCAGTCAGCTGGTCATTTACCAGGTGTGGANTTAAGTTGCTGGGCTTGCAGTAAGAA
TTGCCAGCCANTCATTGTGCG

FIGURE 209

CGTGTGGCCCCCGCGGTGCGGAGTATGGGGCGCTGATGGCCATGGAGGGCTACTGGCGCTTCC
TGGCGCTGCTGGGGTCGGCANTGCTCGTCGGCTTCCTGTCGGTGATCTTCGCCCTCGTCTGGG
TCCTCCACTACCGAGAGGGGCTTGGCTGGGATGGGAGCGCACTAGAGTTTAACTGGCACCCAG
TGCTCATGGTCACCGGCTTCGTCTTCATCCAGGGCATCGCCATCATCGTCTACAGACTGCCGT
GGACCTGGAAATGCAGCAAGCTCCTGATGAAATCCATCCATGCAGGGTTAAATGCAGTTGCTG
CCATTCTTGCAATTATCTCTGTGGTGGCCGTGTTTGAGAACCACAATGTTAACAATATAGCCA
ATATGTACAGTCTGCACAGCTGGGTTGGACTGATAGCTGTCATATGCTATTTGTTACAGCTTC
TTTCAGGTTTTTCAGTCTTTCTGCTTCCATGGGCTCCGCT

FIGURE 210

TTTCATATACCATGGAGTTACATAAAACATGGCATTTTGTATCTGGCTTCTTTCACTTAATGT
TTTCAAGGTTCATTCAGGCTGGAGCGCATAATGATACTTTATTCCTTTCTATGGTTGAATAAT
ATTCCATTGTATGAATAGACCATATTTTGTCTATCCATTCATCAGTTGATGGACATCTGGGTT
ATTTCTATTTTTGGCTATCGTGAATAATGCTGCCATGGACATTCACGTATAAGTTTTTGTGTG
GATATATGTTTTCATTTCTTTGGAGTAGAGTTGCTGGGTCATGGGGTAACCCTAGGTTTAAGC
TTTTGAGGCNTACCAGATTTCCAAAGTGACTGCATCATTTTGCATTCCCATCAACAGTATATG
AAGGTTCTAACTTCTCTACATCTTCACCAATATTTGTTATTGTCTGTCTTCTTGACAAAAGTT
CTCCTAGTGGGTGTGAACTGGTATCATTTTGTGGTTTTGATTTGCATTTCCTGGATGGTTATG
AATGTTGATTTTACTTTCATGTGCTTATTGGCCATTGTATATCTTTGGGAAAATAGCTATTTTCC

FIGURE 211

GTCGAAAGAAGCTTATCTGCAAAAGATATAATGAAAAATGGGAAGAGCAATCATCTCAAACAG
TTCCGGGTTGCTGCCCTTTTGGCTTTCCTAGGTGCTACAGTAGCAGGCTGTTTTCCCCTTTTC
CATAGAGGGGAATATTCTGCATCACCCCTTTGTTTGCCATTTCCTACAGGTGAAACGCCATCA
TTAGGATTCACTGTAACGTTAGTGCTATTAAACTCACTAGCATTTTTATTAATGGCCGTTATC
TACACTAAGCTATACTGCAACTTGGAAAAAGAGGACCTNTCAGAAAACTCACAATCTAGCATG
ATTAAGCATGTCGCTTGGCTAATCTTCACCAATTGCATCTTTTTCTGCCCTGTGGCGTTTTTT
TCATTTGCACCATTGATCACTGCAATCTCTATCAGCCC

FIGURE 212

TTTTGGCCTGTTGGAATTTCCCCANTTTTTTTCCCCAGGAGGATTTGCCCAAAANTGAGCTTN
TATTGGGACAGGNGGCANTTGGATTTTTGGAGTAGGTGGGCTTTTGTTTTTGGGGTCTGCAAT
TGGTTTGTCTTAGAGGTTCAGGAGGGGAAATTATATGGAAGGGTCCCAAATTGCATTACTTTA
CAAACTCATTGTACTCTGTTTGGCCATTAGTCTTCCTTAGGAATCGGACGATTAGCCATTATA
AAATCAATAGGCTATCAGGAACATTTAACAGAGTATTGGAGTTCACTGGAACTTTTTCTTTAC
CATAATAGTTGTGAAATTGATAACACCACTGCTGTTGATTATTTTTCCCCTAAATAAGTCCTG
GATTATTGCCNTCGGCATTACTGTATTATACCAGCTAGCCCTTGACTTTACCTCACTGAAGAG
GTTAATATTATATGGCACTGATGGTAGTGGCACACGGGTTGGTCTATTAAATGCCAACCGCGA
AGGAATAATCTCTACCCTGGGGTATGTGGCAATACACATGGCTGGTGTGCAAACAGGGTTATA
TATGCATAAGAACCGATCACATATCAAAGACTTGATAAAAGTAGCCTGTTTTCTTTTANTGGC
AGCTATTAGCCTCTTCATATCTCTTTACGTAGTTCAAGTAAATGTAGAAGCAGTATCTCGAAG
AATGGCAAATTTAGCCTTTTGTATTTGGATAGTTGCTTCTAGCCTGATCCTTCTTAGTAGTTT
ATTANTGGG

FIGURE 213

GGCGGAACTGAAGTTTTTTCTTAATTATCATGTGACGGGTTCTGGATTTAATGGGGGGAAAAG
GGCGGAATAGGACAAGGATCCAAACTGGCGAATTTGCTGATCTTCGGGTCCCTNTCCGCTTTC
CGGCCGGCAGCGCTGCCAGGGTATATTTCCTTTTTTCCGATCCTGCAACAGCCTNTTTAAACT
GTTTAAATGAGAATGTCCTTGGCTCAGAGNGTACTACTCACCTGGCTTTTCACACTACTCTTC
TTGATCATGTTGGTGTTGAAACTGGATGAGAAAGCACCTTGGAANTGGTTCCTCATATTCATT
CCAGTCTGGATATTTGATACTATCCTTCTTGTCCTGCTGATTGTGAAAATGGCTGGGCGGTGT
AAGTCTGGCTTTGACCCTNGACATGGATCACACAATNTTAAAAAAAAAGCCTGGTACCTCATT
GCAATGTTACTTAAATTAGCCTTCTGCCTCGCACTCTGTGCTAAACTGGAACAGTTTAC

FIGURE 214

NACGGTGAATTTTTNGAAGCCAANGAAGGAGATTTGCACAGGATAGAANTCCCATTCAAATTC
CACATGTTGCATTCAGGGTTGGTCCACGGCNTGGCTTTCTGGTTTGACGTTGCTTTCATCGGN
TCCATAATGACCGTGTGGCTGTCCACAGCCCNGACAGAGCCCCTGACCCACTGGTACCAGGTG
CGGTGCNTGTTCCAGTCACCACTGTTCGCCAAGGCAGGGGACACGCTCTCAGGGACATGTCTG
CTTATTGCCAACAAAAGACAGAGCTACGACATCAGTATTGTGGCCCAGGTGGACCAGACCGGC
TCCAAGTCCAGTAACCTCCTGGATCTGAAAAACCCCTTCTTTAGATACACGGGCACAACGCCC
TCACCCCCACCCGGCTCCCACTACACATCTCCCTCGGAAAACATGTGGAACACGGGCAGCACC
TACAACCTCAGCAGCGGGATGGCCGTGGCAGGGATGCCGACCGCCTATGACTTGAGCAG

FIGURE 215

TGGCCGGATCCCTTTAGAAATCCCTTGGACCTTGGACCCAAGGTGTCCGGGCGAGAGCCTTGG
GATGCACCCGGCCAGAGCCCATGCTGCTGCTGCTNAACGNTTGCCCCTCCNTGGGGGGCCCCA
CTTGGGCAGGGAAGATGTATGGCCCTGGAGGAGGCAAGTATTTCAGCACCANTGAAGATTACG
ACCCATGAAATCACAGGGCTGCGGGTGTCTGTAGGTCTTCTCCTGGTGAAAAGTGTCCAGGTG
AAACTTGGAGACTCCTTGGGACGTGAAACTGGGAGCCTTAGGTGGGAATACCCAGGAAGTCAC
CCTGCAGCCAGGCGAATACATCACAAAAGTCTTTGTCGCCTTCCAAGCTTTCCTCCGGGGTAT
GGTCATGTACACCAGCAAGGACCGCTATTTCTATTTTGGGAAGCTTGATGGCCAGATCTCCTC
TGCCTACCCCAGCCAAGAGGGGCAGGTGCTGGTGGGCATCTATGGCCAGTATCAACTCCTTGG
CATCAAGAGCATTGGCTTTGAATGGAATTATCCACTAGAGGAGCCGACCACTGAGCCACCAGT
TAATCTCACATACTCAGCAAACTCACCCGTGGGTCGCTAGGGTGGGGTATGGGGCCATTTACC
GAGCGGCCGCCGTAATTGGGCCGCTGGGGTATCTCTCGAGAAAAGAGAGGCCCAATATGACCC
ACATACTCAATATGGACGAACTGATATTGTCCACCTGTTATGAGTG

FIGURE 216

TTTCCAAAAGTTGTGAAGGACACCTCCATCCATTCAAGGCAGTTGTCAAAGCAGAAATTTTCA
GTGCAAGTCTTGATGTTGCCCCGTCCCCNATTCCCTACATCAGAAGGATCCCTCATNTGGACT
CCAGCGTTGGCTTCTTGATGCTGCGCGTTCCCCCATTCCCTACATCAGAATGCATCCCGCATC
CAGACTCCAGCGTTGNTGCTCTACNTGCACGCTGTTGCCAAGTCCAAGNTACCATACTCCTGC
CTGAGCTATGACAACAGCCTCCTCACTGATCTCCCCTTTCTTCCCTTTGCCTCCTCCAGCTCA
TTTTTCACAGTGTAGAATGACATTTTGTTTGTNTGTTNTGTTNTGTTTGAGATGGAGTCTCGC
TCTGTTGCCCAGGGTGGAGTGCAGCGGTGCGATCTCGGCTCACTGCAACCTCCACCTCCCGGG
TTCAAGCGGATTCTCGTGCCTCAGCCTCCTGAG

FIGURE 217

CACAGTTCCCCACCATCACTCNTCCCATTCCTTCCAACTTTATTTTTAGCTTGCCATTGGGAG
GGGGCAGGATGGGAGGGAAAGTGAAGAAAACAGAAAAGGAGAGGGACAGAGGCCAGAGGACTT
CTCATACTGGACAGAAACCGATCAGGCATGGAACTCCCCTTCGTCACTCACCTGTTCTTGCCC
CTGGTGTTCCTGACAGGTCTCTGCTCCCCCTTTAACCTGGATGAACATCACCCACGCCTATTC
CCAGGGCCACCAGAAGCTGAATTTGGATACAGTGTCTTACAACATGTTGGGGGTGGACAGCGA
TGGATGCTGGTGGGCGCCCCCTGGGATGGGCCTTCAGGCGACCGGAGGGGGGACGTTTATCGC
TGCCCTGTAGGGGGGGCCCACAATGCCCCATGTGCCAAGGGCCACTTAGGTGACTACCAACTG
GGAAATTCATCTCATCCTGCTGTGAATATGCACCTGGGGATGTCTCTGTTAGAGACAGATGGT
GATGG

FIGURE 218

CTCTTAGGCTTTGAAGCATTTTTGTCTGTGCTCCCTGATCTTCATGTCACCACCATGAAGTTC
TTAGCAGTCCTGGTACTCTTGGGAGTTTCCATCTTTCTGGTCTCTGCCCAGAATCCGACAACA
GCTGCTCCAGCTGACACGTATCCAGCTACTGGTCCTGCTGATGATGAAGCCCCTGATGCTGAA
ACCACTGCTGCTGCAACCACTGCGACCACTGCTGCTCCTACCACTGCAACCACCGCTGCTTCA
ACCACTGCGACCACTGCTGCTCCTACCACTGCAACCACC

FIGURE 219

CGGGCTTTGAAGCATTTTTGTCTGTGCTCCCTGATCTTCAGGTCACCCCCATGAAGTTCTTAG
CAGTCCTGGTACTCTTGGGAGTTTCCATCTTTCTGGTCTCTGCCCAGAATCCGACAACAGCTG
CTCCAGCTGACACGTATCCAGCTACTGGTCCTGCTGATGATGAAGCCCCTGATGCTGAAACCA
CTGCAACTGCAACCACTGCGACCACTGCTGCTCCTACCACTGCAACCACCGCTGCTTCTACCA
CTGCTCGTAAAGAC

FIGURE 220

GGCTTTGAAGCATTTTTGTCTGTGCTCCCTGATCTTCAGGTCACCCCCATGAAGTTCTTAGCA
GTCCTGGTACTCTTGGGAGTTTCCATCTTTCTGGTCTCTGCCCAGAATCCGACAACAGCTGCT
CCAGCTGACACGTATCCAGCTACTGGTCCTGCTGATGATGAAGCCCCTGATGCTGAAACCACT
GCAACTGCAACCACTGCGACCACTGCTGCTCCTACCACTGCAACCACCGCTGCTTCTACCACT
GCTCGTAAAGAC

FIGURE 221

TGATTTTTACACACCCCAGGATTTTTTGGAATTGAGGAGACGGTTCAAGAGTTTAGCCTTGGA
NTGGCCCAGTATCCAGGTCGAGGTTCTGCAGAAGGTTGTGACTTTAGTAACATTTTTCTTCTT
TCGGGGACGTGGCCTGCATGGCTATCTGCTCCTGCCAGTGTCCAGCAGCCATGGCCTTNTGCT
TCCTGGAGACCNTGTGGTGGGAATTCACAGCTTCCTATGACACTACCTGCATTGGCCTAGCCT
CCAGGCCATACGCTTTTCTTGAGTTTGACAGCATCATTCAGAAAGTGAAGTGGCATTTTAACT
ATGTAAGTTCCTCTCAGATGGAGTGCAGCTTGGAAAAAATTCAGGAGGAGCTCAAGTTGCAGC
CTCCAGCGGTTCTCACTCTGGAGGACACAGATGTGGCAAATGGGGTGATGAATGGTCACACAC
CGATGCACTTGGAGCCTGCTCCTAATTTCCGAATGGAACCAGTGACAGCCCTGGGTATCCTCT
CCCTCATTCTCAACATCATGTGTGCTGCCCTGAATCTCATTCGAGGAGTTCACCTTGCAGAAC
ATTCTTTACAGGTTGCCCATGAGGAAATTGGAAACATTCTGGC

FIGURE 222

CGAAGGCTTGGGCGGANGCGTGGGCGCGGGAGTGCATGGCAGNTTTGGTTCCCAGACTTGCCC
GGACCCNTTTGCTTCACCTCCAGCTNTGNTGCTCCTNTACTCTTGGGTCGAGATCCCTTTGGA
GCCACAGCGAGGAACCCTGTGGTCCTCAGGCAGGTGTACCTTGAGTCAGCCCAGGAGCCCTCT
TTTCNTGTGTCAAAGCCTGCCCTCGGGCTNTGCTCACCTNTGGTGACCCTCCCAAGATGCCCC
TGCCCTCAGTTTCCCCTCATGATCTGGCCTCTGCCCCCTTCTNTAGCCACAGCCTTTTAGTAC
ACTTTAGCAATNNCNACCNGAANTAGTTNGAGTTCCCCAATTCACCAAGCAAGACATGCAGTT
TCATGCCTCTGTGCCTTCGCTCATGCTTGTTTCTTCCGAACTTGGAATGCCTTCCCCTGCTCC
TCCTGCCTTGTCTGCCTGGCAAGTTCATCTCTCACGATCCCCTCAAAGGCCCCCTCCTCCAGG
AAGGCAACCCCTGTGCCCCTCCCCTCCAGGCTACCTCTGCACTTTGTCAATGCTTCTCTTGTG
GCACTTATCACACTGTATTTTACTTGTTTACATGTTTGTCTCCCC

FIGURE 223

NCCAATGCAGGCCTCCGGTTNTCCGCGAAGAAGTTCCTTGCCCCGATGAGCCCCCGCCGTGCG
TCCCCGATTATCCCCAGGCGGGCGTGGGGCACCGGGCCCAGCGCCGACGATCGCTGCCGTTTT
GCCCTTGGGAGTAGGATGTGGTGAAAGGATGGGGCTTCTCCCTTACGGGGCTCACAATGGCCA
GAGAAGATTCCGTGAAGTGTCTGCGCTGCCTGCTNTACGCCCTCAATCTGCTCTTTTGGTTAA
TGTCCATCAGTGTGTTGGCAGTTTCTGCTTGGATGAGGGACTACCTAAATAATGTTCTCACTT
TAACTGCAGAAACGAGGGTAGAGGAAGCAGTCATTTTGACTTACTTTCCTGTGGTTCATCCGG
TCATGATTGCTGTTTGCTGTTTCCTTATCATTGTGGGGATGTTAGGATATTGTGGAACGGTGA
AAAGAAATCTGTTGCTTCTTGCATGGTACTTTGGAAGTTTGCTTGTCATTTTCTGTGTAGAAC
TGGCTTGTGGCGTTTGGACATATGAACAGGAACTTATGGTTCCAGTACAATGGTCAGATATGG
TCACTTTGAAAGCCAGGATGACAAATTATGGATTACCTAGATATCGGTG

FIGURE 224

TAAGTTCCTGCATTAAAACCATGCTGTNGCAATTGAGAGCTTAGCTCCACGGTTCTCAAAGGG
AGGTCCCTGGCCAACAGCATCAGCATCACCTTGAGGACNTANTNGCAATGCAAATTATCAGGG
CCCTTCTTCAGACTCACTGAATCAGAAACCNTGGGATAGGNCCAGCACGCTGTGCTTTAACAA
GCTCTAGGTGATGCCCAATTCATACTCAAGTGTGAGGCTGACTGGCTTATTTGAAGGGAGAGA
AAGGAACAGGCACATGGCGACATATCAGCATTTACACAAGGCGTGCTGGGTAACCATAGGAAC
ACCTTTATTACGGTTAAATAGGAAACAGGCATCAATGCAGAGGGCCCCCAGGAGAATCAGGAA
GGTCGCGACTGTCACTGTCTGAGGGCACTGTTGTGAAACGATGGCCGAAGGTGACAACCACAG
CAAAGTTTCAAGGAAGTTCACTGAAACGTGGAAAAACCCACTCAATGTCCTGCTCTCATTTAT
ATTGAGTGGCTTAAGTATTTATTTTCTTGGTTTTTTAGAGGAAGGGAGGGTTGGAGGATTCTC
AAAGCATTCAAAAGGACACCATATGCTGGCAGGAAATATTCAAGCTTTTAATGGAATAATGCA
ATGGAGGTG

FIGURE 225

TACCCTTGGCCACTTAAGTTGGAGAAATTTGAAATCAAGAAGTTNTCATTTTGAAGAAGCACG
AGTTCGGAAGACTTTAACATGGGTTNTTCCTTNTTGCAGCCNGTATACTTTNTGTCANCCAGA
AACTGTATTTTCATNTCAGCNTAGTGACGATGAATCAAGTAGTGATGAACCNGTAATCAGCCC
AGTCNTGCCTTTAGANGACNCCGTGTTAGGAAGAAGACCGTTTNTGNTTCAGAATNTGAAGAC
CGGNTAGTTGCTGAACAAGAAACTGAACCTTNTAAGGAGTTGAGTAAACGTCAGTTCAGTAGT
GGTCTCAATAAGTGTGTTATACTTGCTTTGGTGATTGCAATCAGCATGGGATTTGGCCATTTC
TATGGCACAATTCAGATTCAGAAGCGTCAACAGTTAGTCAGAAAGATACATGAAGATGAATTG
AATGATATGAAGGATTATCTTTCCCAGTGTCAACAGGAACAAGAATCTTTTATAGATTATAAG
TCATTGAAAGAAAATCTTGCAAGGTGTTGGACACTTACTGAAGCAGAGAAGATGTCCTTTGAA
ACTCAGAAAACGAACCTTGCTACAGAAAATCAGTATTTAAGAGTATCCCTGGAAAAGGAAGAA
AAAGCCTTATCCTCATTACAGGAAGAGTTAAACAAACTAAGAGAACAGATTAGAATATTGGAA
GATAAAGGGAC

FIGURE 226

GGTCCCCAACGGGCCCCCCGGGTCGGTTTNCCGCGTTGGCCATGANTGCGNCCGTGTTCTTTC
GGNTGCGCCTTCATTTGCCTTCGGGCNTGCGNTCGCCCTTTATGTCTTCACCATCGCCATCGA
GCCGTTGCGTATCATCTTCCTCATCGCCGGAGCTTTCTTCTGGTTGGTGTCTNTACTGATTTC
GTCCCTTGTTTGGTTCATGGCAAGAGTCATTATTGACAACAAAGATGGACCAACACAGAAATA
TCTGCTGATCTTTGGAGCGTTTGTCTCTGTCTATATCCAAGAAATGTTCCGATTTGCATATTA
TAAACTCTTAAAAAAAGCCAGTGAAGGTTTGAAGAGTATAAACCCAGGTGAGACAGCACCCTC
TATGCGACTGCTGGCCTATGTTTCTGGCTTGGGCTTTGGAATCATGAGTGGAGTATTTTCCTT
TGTGAATACCCTATCTGACTCCTTGGGGCCAGGCACAGTGGGCATTCATGGAGATTCTCCTCA
ATTCTTCCTTTATTCAGCTTTCATGACGCTGGTCATTATCTTGCTGCATGTATTCTGGGGCAT
TGTATTTTTTGATGGCTGTGAGAAGAAAAAGTGGGGCATCCTCCTTATCGTTCTCCTGAC

FIGURE 227

GACCAAGGGTCCGGGTAGNTTACCTATATTTGGTTNATGGTNTAATTATAGACCAGGAAAGAG
CNTNTTATGTCTCCATCTTGATTTCCGTGGCAGCCAANTGCCTNTATGNATATCTCCACATCC
CAGCTTTTTCATAATAAATANTACATGCTGGTTGCTCGTGGATTGTTGGGAATTGGAGCAGGA
AATGTAGCAGTTGTTAGATCATATACTGCTGGTGNTACTTCCCTTCAGGAAAGAACAAGTTCC
ATGGCAAACATAAGCATGTGTCAAGCATTAGGTTTTATTNTAGGTCCAGTTTTTCAGACTTGT
TTTACATTCCTTGGAGAAAAAGGTGTGACATGGGATGTGATTAAACTGCAGATAAACATGTAT
ACAACACCAGTTTTACTTAGCGCCTTCCTGGGAATTTTAAATATTATTCTGATCCTTGCCATA
CTAAGAGAACATCGTGTGGATGACTCAGGAAGACAGTGTAAAAGTATTAATTTTGAAGAAGCA
AGTACAGATGAAGCTCAGGTTCCCCAAGGAAATATTGACCAGGTTGCTGTTGTGGCCATCAAT
GTTCTGTTTTTTGTGACTCTATTTATCTTTGCCCTTTTTGAAACCATCATTACTCCATTAACA
ATGGATATGTATGCCTG

FIGURE 228

TGAAATTATTAAACCAAACAAACAAACAAAAACCCGGAATGCATTGTATAGGATTGCATGTGA
AGTCTTTTNTANTGAATNTATATTTCCANTTGAAGTGATTTTAAGTTAACATNTGAAGGCAGG
AAATGATTNCCTTTCCAGTAAAAAGTNTAGNTAATTTAATTAANTTAGTGACACCACCAAGTG
TTTTGATATAACTAAATTTGTGGTAATAAGATTGTCTGCACCTGTATTCATTGTGGAANTTCC
TCTTTCATTGGAAANTTTNTTACTCAAGAATGACGGCAGTATTGTTTTCTTATATGTGCAATG
AAGTGGAATGGTTAACNGTATGCCCTTAAATTTAAAATGGGTTCCTTGTTCTGATGTTGTTTC
CTGAAATGATTTTTCTTCCTAACTGTGGTTTTCGGGTATGCAAGCCTAAATCTTTGTACACTT
TGTCTCACAGAATAGTTCTGAGGCTCCATGACAGGGTTTTGTCATTGTTGATGTTANTGTTGC
TTCGTTTTATAAAAAAGCCAAAATTTTTTTCCAATCCAAACGTTCACCTGTTTCCTTTCCTCA
AGNTATACCAGTGTAATACCAGTTACCCTGTGGATCCATTTAATATGTTATCCCCACTAATTA
ATTTTCGTATATTATTTCCAATATTTGGAAAGCTCTTTATAGCCATTTGGTATTTCCTATTAC
CCAC

FIGURE 229

TTTTCAATTTGCCAGTTTGTGGATGATGAATTGACTTAAATCGAACTAAATTGGAATGTGAAT
CTGCATGTACGAAGCATATTCCCAATNTGATGAGCAATATGCTTGCCATCTTGGTTGCCAGAA
TCAGTTCCATTCGCTGAANTGGACAAGAACAACTTATGTCCCTGATGCCAAAAATGCACCTAN
TCTTTCCTCTAACTCTTGGTGAGGTCATTCTGGAGTGACATGATGGACTCCGCACAGAGNTTC
ATAACCTCTTCATGGACTTTTTATCTTCAAGCCGATGACGGAAAAATAGTTATATTCCAGTTT
AAGCCAGAAATCCCAGTACGCACCACATTTGGAGCAGGAGCCTACAAATTTGAGAGAATCATC
TCTAAGCAAAATGTCCTATCTGCAAATGAGAAATTCACAAGCGCACAGGAATTTTCTTGAAGA
TGGAGAAAGTGATGGCTTTTTAAGATGCCTCTCTCTTAACTCTGGGTGGATTTTAACTACAAC
TCTTGTCCTCTCGGTGATGGTATTGCTTTGGATTTGTTGTGCAACTGTTGCTACAGCTGTGGA
GCAGTATGTTCCCTCTGAGAAGCTGAGTATCTATGGTGACTTGGAGTTTATGAA

FIGURE 230

TCCTGCTGATGCACATCTGGGTTTGGCAAAAGGAGGTTGCTTCGAGCCGCCCTTTCTAGCTTC
CTGGCCGGCTCTAGAACAATTCAGGCTTCGCTGCGACTAGACCTCAGCTCCAACATATGCATT
CTGAAGAAAGATGGCTGAGATGACAGAATGCTTTATTTTGGAAAGAAACAATGTTCTAGGTCA
AACTGAGTCTACCAAATGCAGACTTTCACAATGGTTCTAGAAGAAATCTGGACAAGTCTTTTC
ATGTGGTTTTTCTACGCATTGATTCCATGTTTGCTCACAGATGAAGTGGCCATTCTGCCTGCC
CCTCAGAACCTCTCTGTACTCTCAACCAACATGAAGCATCTCTTGATGTGGAGCCCAGTGATC
GCGCCTGGAGAAACAGTGTACTATTCTGTCGAATACCAGGGGGAGTACGAGAGCCTGTACACG
AGCCACATCTGGATCCCCAGCAGCTGGTGCTCACTCACTGAAGGTCCTGAGTGTGATGTCACT
GATGACATCACGGCCACTGTGCCATACAACCTTTGTGTCAGGGCCACATTGGGCTCACAGACC
TCAGCCTGGAGCATCCTGAAGCATCCCTTTAATAGAAACTCAACCATCCTTACCCGACCTGGG
ATGGAGATCACCAAAGATGGCTTNCACCTGGTTATTGAGCTGGAGGACCTGGGGCCCCAGTTT
GAGTTCCTTGTGGCCTANTGGAGGAGGGGCGAACCCCTTGCGGCGCAAGGGGTTNGCGAACCC
CTTGCGGCCGCTGGGGTATCTCTCGAGAAAAGAGAGGCCCAATATGACCCACATACTCAATAT
GGACGAANTGCTATTGTCCACCTGTTTGAGTGGCGCTGGGTTGAT

FIGURE 231

TAGAGCGACAGTGGAAGGGGCATGACCCTCAATGAGGACGGCCTTGTTTCCTGGGAGGNGTNT
AAAAATTCCAACCTACGGNTACGTTTTAGATGATCCAGATCCTGATGATGGATTCAANTATAA
ACAGATGATGGTTAGAGATGAGCGGAGGTTTAAAATGGCAGACAAGGATGGAGACCTCATTGC
CACCAAGGAGGAGTTCACAGCTTTCCTGCACCCTGAGGAGTATGACTACATGAAAGATATAGT
AGTACAGGAAACAATGGAAGATATAGATAAGAATGCTGATGGTTTCATTGATCTAGAAGAGTA
TATTGGTGACATGTACAGCCATGATGGGAATACTGATGAGCCCAGAATGGGTAAAGACAGAGC
GAGAGCAGTTTGTTGAGTTTCGGGATAAGAACCGTGATGGGAAGATNGACAAGGAAGAGACCA
AAGANTGGATCCTTCCCTCAGACTATGATCATGCAGAGGCAGAAGCCAGGCACCTGGTCTATG
AATCAGACCAAAACAAGGNTGGCAAGCTTACCAAGGAGGAGATCGTTGACAAGTATGANTTAT
TTGTTGGCAGCCAGGCCACAGATTTTGG

FIGURE 232

ACCGCCTTCAGTTACTCCAGGTAGCCCCGTAGCATTTAAAGAACAAAATCTGTCCAGTCAAAG
TGATTTTCTTCAAGAGCCGTTACAGGNTACTTCTTNTCCAGTTACTTGTAGCTCAAATGCTTG
CTTGGTTACTACCGATCAGGNTTCTTCTGGATCTGAAACAGAGTTTATGACCTCAGAGACTCC
TGAGGCAGCAATTCCCCCAGGCAAGCAACCGTNTTCACTAGCTTNTCCAAATCCTCCCATGGC
AAAGGGCTCTGAACAGGGNTTCCAGTCACCTCCAGCAAGTAGTAGTTCAGTAACCATTAACAC
AGCACCCTTTCAAGCCATGCAGACAGTATTTAACGTTAATGCACCTCTGCCTCCACGAAAAGA
ACAAGAAATAAAAGAATCCCCTTATTCACCTGGNTACAATCAAAGTTTTACCACAGCAAGTAC
ACAAACACCACCCCAGTGC

FIGURE 233

CGGGAANCCCGANCCGGTTGCCCCGGGGAANCCGTGCGGCCCCTTCCGTCCCGTTCCCATCCT
TGCCGGGGTTCCAGCACCTTTGAAGTTTTTGCAGCGCCCGAAANGGAGGCGAGGAAGGAGGGA
NTNTNTGAGAGGAGGGAGCAAAAAGCTTCACCNTAAAACATTTATTTCAAGGAGAAAAGAAAA
AGGGGGGGCGCAAAAATGGCTGGGGCAATTATAGAAAACATGAGCACCAAGAAGCTGTGCATT
GTTGGTGGGATTCTGCTCGTGTTCCAAATCATCGCCTTTCTGGTGGGAGGCTTGATTGCTCCA
GGGCCCACAACGGCAGTGTCCTACATGTCGGTGAAATGTGTGGATGCCCGTAAGAACCATCAC
AAGACAAAATGGTTCGTGCCTTGGGGACCCAATCATTGTGACAAGATCCGAGACATTGAAGAG
GCAATTCCAAGGGAAATTGAAGCCAATGACATCGTGTTTTCTGTTCACATTCCCCTCCCCCAC
ATGGAGATGAGTCCTTGGTTCCAATTCATGCTGTTTATCCTGCAGCTGGACATTGCCTTCAAG
CTAAACAACCAAATCAGAGAAAATGCAGAAGTCTCCATGGACGTTTCCCTGGCTTACCGTGAT
GACGCGTTTGCTGAGTGGACTGAAATGGCC

FIGURE 234

TTTGTTTCCCGGGACCTTGGTGGCAGTTCTGCAGCCACAGAGGCAGTGGCGATTTTGACAGCC
ACATACCNTGTGGGTCACATGCCATACGGCTGGTTGACGGAAATCCGTGCTGTGTATCCTGCT
TTCGACAAGAATAACCCCAGCAACAAACTGGTGAGCACGAGCAACACAGTCACGGCAGCCCAC
ATCAAGAAGTTCACCTTCGTCTGCATGGCTCTGTCACTCACGCTCTGTTTCGTGATGTTTTGG
ACACCCAACGTGTCTGAGAAAATCTTGATAGACATCATCGGAGTGGACTTTGCCTTTGCAGAA
CTCTGTGTTGTTCCTTTGCGGATCTTCTCCTTCTTCCCAGTTCCAGTCACAGTGAGGGCGCAT
CTCACCGGGTGGCTGATGACACTGAAGAAAACCTTCGTCCTTGCCCCCAGCTCTGTGCTGCGG
ATCATCGTCCTCATCGCCAGCCTCGTGGTCCTACCCTACCTGGGGGTGCACGGTGCGACCCTG
GGCGTGGGCTCCCTCCTGGCGGGCTTTGTGGGAGAATCCACCATGGTCGCCATCGCTGCG

FIGURE 235

CGGACGCGTGGGTTTAAAAATTACTCATAATCGNTCCATTGATAATACTAAATTTAGTTTCCC
CTGTCTTTAGTGTCTAATTGTCAGCCAGAAAATTAGGAATCTGTTGCACTTGATTTTTAAGTA
ACTTATCTAAAACTATGTGCCATTTTAACAGTGAGCATTACTTAGTTGCATTTTCCAAATTTA
TTATTTNNTCATTTCTTAACTGTAGACTATTATTTCAAAATTTTAAATTTAGTTTTTGATGTT
TTAGAGAAATGAAGCCACAGTGGCTTAGCACATCTTTGTGTTTCTATTATTTATNTATTTTTT
TGAGACAGAGTCTTGCTGTGTTGCTCAGGCTGGAGTGCAGTGGTGCGATCTCAGCTCACTGCA
ACCTCTGCCTCCCGGGTTCAAGTGATTTTCCTGCCTCAGCCTCCCAAGTAGCTGGGATTACAG
ACACCTGCCACCATGTCCGG

FIGURE 236

GAGGTCATCTCCATTTCATCCCGGATAAATGAGTATGCAAGGAACGTTTTTATAGGCATTTTG
GAGATCAAAGATGGGTAGAAAAGATGCTGNTACTATAAAACTTCCTGTTGATCAGTACAGAAA
ACAAATTGGTAAACAGGATTATAAAAAAACTAAACCTATTTTACGAGCTACCAAATTAAAAGC
AGAAGCAAAGAAAACAGCAATAGGCATAAAGGAAGTTGGCCTTGTACTTGCAGCTATATTGGC
ACTACTACTGGCTTTCTATGCTTTCTTTTATCTCAGACTCACCACGGAAATGTTG

FIGURE 237

CGGGGGAACCCGAGCCGGTTGCGCCGGGGGAATCCGTGCGGGCGCCTTCCGTNCCGGTCCCAT
CCTNGCCGCGCTCCAGCACCTTTGAAGTTTTGCAGCGCCCAGAAAGGAGGCGAGGAAGGAGGG
AGTGTGTGAGAGGAGGGAGCAAAAAGCTCACCCTAAAACATTTATTTCAAGGAGAAAAGAAAA
AGGGGGGGCGCAAAAATGGCTGGGGCAATTATAGAAAACATGAGCACCAAGAAGCTGTGCATT
GTTGGTGGGATTCTGCTCGTGTTCCAAATCATCGCCTTTCTGGTGGGAGGCTTGATTGCTCCA
GGGCCCACAACGGCAGTGTCCTACATGTCGGTGAAATGTGTGGATGCCCGTAAGAACCATCAC
AAGACAAAATGGTTCGTGCCTTGGGGACCCAATCATTGTGACAAGATCCGAGACATTGAAGAG
GCAATTCCAAGGGAAATTGAAGCCATA

FIGURE 238

TCCATAATGACCGTGTGGNTGTCCACAGCCCCGACAGAGCCCCCTGACCCAATTGTACCAGGT
GCGGTGCCTGTTCCAGTCACCATTGTTCGCCAAGGCAGGGGACACGNTTTCAGGGACATGTTT
GNTTATTGCCAACAAAAGACAGAGNTACGACATCAGTATTGTGGCCCAGGTGGACCAGACCGG
CTCCAAGTCCAGTAACCTCCTGGATNTGAAAAACCCCTTNTTTAGATACACGGGCACAACGCC
CTCACCCCCACCCGGNTCCCANTACACATNTCCCTCGGAAAACATGTGGAACACGGGCAGCAC
CTACAACCTCAGCAGCGGGATGGCCGTNGCAGGGATGCCGACCGCCTNTGACTTGAGCAGTGT
TATTNCCAGTGGCTCCAGCGTGGGCCACAACAACCTGATTCCTTTAGGGTCCTCCGGCGCCCA
GGGCAGTGGTGGTGGCAGCACGAGTGCCCACTATGCAGTCAACAGCCNG

FIGURE 239

TTCCCCTAATGGGTTGTTTGACCCCCATTCCGGTTGNTAAGTGGTTTTTCCCNATCATCGGCC
AAATTGGNATTTTCANATCCACAGGNGTCATTGGGANTTTGGGGGCCCCTAATTTGTTTCAGA
CAGGCCGGGAGGCAGTTTGCCAGAAGGATTCTTAAGTAANTGACCCAGCCCTTTGCCCCCACC
CCTGGGGTACCGAGACATGGGTAGGGATTAGAGCAAGAGTTGAGAGTCAGACCATCCAGGAAC
CACATNTNTGGACCTTCAGAAGGAGGACAACATGGCCTTTGGAAAGCCTNCCAAGTACTGGAA
GTTGGACCCTGNTCAGGTNTATGCTAGCGGGCCCAACGCATGGGACACGGCTGTGCACGACGC
CTCTGAGGAGTACAAGCACCGCATGCACAATCTCTGCTGTGACAACTGCCACTCGCACGTGGC
ATTGGCCCTGAATCTGATGCGCTACAACAACAGCACCAACTGGAATATGGTGACGCTCTGCTT
CTTCTGCCTGCTCTACGGGAAGTACGTCAGCGTTGGGGCCTTCGTGAAGACCTGGCTGCCCTT
CATCCTTCTCCTGGGC

FIGURE 240

TTTTTCAGGGAGAATTTTGAGGCTNTGTTGAGAATCATGCTTTGGAGGCAGCTCATNTATTGG
CAACTGCTGGCTTTGTTTTTCCTCCCTTTTTGCNTGTGTCAAGATGAATACATGGAGGTGAGC
GGAAGAACTAATAAAGTGGTGGCAAGAATAGTGCAAAGCCACCAGCAGACTGGCCGTAGCGGC
TCCAGGAGGGAGAAAGTGAGAGAGCGGAGCCATCCTAAAACTGGGACTGTGGATAATAACACT
TNTACAGACCTAAAATCCCTGAGACCAGATGAGCTACCGCACCCCGAGGTAGATGACCTAGCC
CAGATCACCACATTCTGGGGCCAGTNTCCACAAACCGGAGGACTACCCCCAGACTGCAGTAAG
TGTTGTCATGGAGACTACAGCTTTCGAGGCTACCAAGGCCCCCCTGGGCCACCGGGCCCTCCT
GGCATTCCAGGAAACCATGGAAACAATGGCAACAATGGAGCCACTGGTCATGAAGGAGCCAAA
GGTGAGAAGGGCGACAAAGGTGACCTGGGGCCTCGAGGGGAG

FIGURE 241

GGTGATCTGAAAGATAGCCAAGGATTTTTCAGAACACAAGAAAAAAGAGGGATGAAAAGTGAA
AAAGAAATTAGAAGATATGGATAATAAATCCCAGGAGAGGTAATATGCATCCAATCAAACATN
TAATAGAAAATTTCCTACAGGGAATAAAAGAAAAAGATTCTTAAGATCGAAAGGGCCAGTTGA
TAGTGGTACCCAGGAGGAAGGAGTGGTTTTTCACCCAGATATATCCTGGTGAAATTTCTGAAT
TCTGCAGCTTACAAGAAAATTCTGAACTCTTCCAGGGAAGAACAAGCTATGTACAAAGGAATA
AGAATCTTATTCATTACACTAAAGACAATGCTTTTGATCATTGTCTATAGCTATGTGTATTTT
GAACCTAGAATTCCGTACTCAGCCCAACTGTCATTTATGTATGAGAACAAAATTAACTTTTTG
GAATTTGCAGACTCATATTCTTTTCGAAAAAAATACTGTGGGATGTACCAAAACAAAAAAATA
AGTCAAGAAGCAACAACTCAAGGCATAAGAAACAGTAGCGAG

FIGURE 242

TTCCAGAGAGCCCTTGAGAAGACCAAGGGCAAAGTGAGCATGAGGTTCTCCTCTCTCTGCCCA
CCCTCCACGTCCACTGCCTCTGGCCGCAGACCCAGCNTCGTGATCGATGGGAGAAGCNTGGCC
TACGCTCTCGAGAAAAACCTGGAGGACAAATTCCTCTTCCTTGCCAAGCAGTGCCGCTCCGTC
CTCTGCTGTCGGTCGACGCCTCTGCAGAAGAGCATGGTGGTGAAGCTGGTGCGGAGCAAGCTC
AAGGCCATGACCCTGGCCATAGGTGATGGAGCCAATGATGTCAGCATGATCCAGGTGGCAGAT
GTGGGTGTGGGAATCTCCGGCCAGGAGGGTATGCAGGCAGTGATGGCCAGCGACTTTGCAGTG
CCGAAATTCCGATACCTGGAGAGGCTCTTGATTCTTCACGGGCATTGGTGCTACTCCCGACTT
GCCAACATGGTGCTGTACTTCTTCTACAAAAACACAATGTTCGTGGGCCTCCTGTTTTGGTTC
CAGTTTTTCTGTGGCTTCTCTGCATCTACCATGATTGACCAGTGG

FIGURE 243

TTCCCAGCGAGGATCCTGTCCCTGGAGGCTGTAATTTGGAGTTCGATTTAGATATTGATCCCA
ACATTTACTTGGAGTATAATTTCTTTGAAACGANTATCAAGTTTGCCCCAGCAAACNTAGGCT
ATGCGAGAGGCGTAGATCCCCCACCATGTGACGCTGGGACAGACCAGGACTCCAGGTGGAGGT
TGCAGTATGATGTCTATCAGTATTTTCTGCCTGAGAATGACCTCACTGAGGAGATGTTGCTGA
AGCATCTGCAGAGGATGGTCAGTGTGCCCCAGGTGAAGGCCAGTGCTCTCAAGGTGGTTACCC
TAACAGCTAATGATAAGACAAGTGTTTCCTTCTCCTCCCTCCCGGGACAAGGTGTCATATACA
ATGTCATTGTTTGGGACCCGTTTCTAAATACATCTGCTGCCTACATTCCTGCTCACACATACG
CTTGCAGCTTTGAGGCAGGAGAGGGTAGTTGTGCTTCCCTAGGAAGAGTGTCTTCCAAAGTGT
TCTTCACTCTTTTTGCCCTGCTTGGTTTCTTCATTTGTTTCTTTG

FIGURE 244

ATTCTTAAGTCAGTTGATCCANTTATTCATTCATCAAATATTGATTGAGAACCTACTGTGTGC
CAAGTGTTATTTTAGGCCCTGGGACCAAGTAATAAATAAGAGGACACAGGCCATGCACTCACG
GAGCTTCTGTTTTCCTTGGCAGAGCAGACATGGGGCAGGGTGGTCTGAGGGTCTCCTCAGGAT
GGTGTGGTCTGTGCTGGTTGTGGTTGTCTTGACAGGTTGGGCCTCATGGGCAGATGGTACCTG
TCAGGCAGGGAGTGTGGGGGCAACCAGGATGAACAGTTATAAGACCATTTCTAATACTTGTAT
TTTTTTTTCTCCTAGGGAAAAATTGGAAGAAAAAGCCAAATTATATGAAAAAATGACTAAAGG
AGACTTTATAGATGAAGAAGTAGAGGATATGTACCTTGTGGATTTCACACAGAAGATCATAGA
CAAGCGC

FIGURE 245

GGNTACCCGAAGGCCAAGCTTTTTAACAATTTTGNTTTGTAATCAATGNGTAATTCATGATGA
ATTATTTTGACTAATGGNTAGCCGAAGGCCAAGCTTTTAATTNTAATAGGTAATGTTCTTCTT
TTGTCTTATTGAAACAATGNGAATANTCTGTGCATTTCAAATGCACTCCGATTATGCTGTGGT
TTTATTCACATAAGCACAATATGTGTTTTATTTATAANTTCATAACAAANTTATAATATAATA
ATTTACCTTAGCAGACATGCAAAAGCTTATTCTTGTGTGANTTACTTTCTTTAAGNTAATAAT
ATAAAAATAAATATGTATCTTAAAAATCTATAATAAAACATTNGAAATTAAAGATATGTGCTT
TTTATTTTGCAGATGAGTTCATTTGCTTCTGTAGATGTGTTTTCAGAGNTAGGTACAGAGGAA
TGTTTGNTACCTTTAGCGGTGAAAAAAGAAAGAGNGTCNAGAATTTTGTTGGATTGTGTTTGT
GTGTGCATATATTTGATATCATCATCATACATTGTAATCTTTGGACTTGTAATCATAGCCTNN

FIGURE 246

TTCCCACTGTAATGCCAAATGATCCATAGCCTNTTCAGATTCCTTATAAAATTTAAACCAAGA
GAGGAGAGGAAAGGGTAAATTTTCTGTAATGACCTTNTGCTTAATAGTCTTNTAGAAAAAGGA
AAGGTGATGAGCAAATAAAGGAACTTNTAGANTTTACATGACTAGGCTGATAATCTTANTTTT
TAGGNTTCTATACAGTTAATTCTATAAATTCTCTTTCTCCCTCTCTTCTCCAATCAAGCACTT
GGAGTTAGATNTAGGTCCTTNTATCTCGTCCCTNTACAGATGTATTTTCCACTTGCATAATTC
ATGCCAACANTGGTTTTCTTAGGTTTCTCCATTTTCACCTCTAGTGATGGCCCTANTCATATC
TTCTCTAATTTGGTCCTGATANTTGNTTCGTNTCACGTTTTCCCATTTCCCTGTGGCTCACTG
TTTTACAATCACNGCTNTGGAATCATGATACCACTTTTAGCTCNTTGCATCTTCCTTCAGTGT
ATTNTTGTTTTTCAAGAGGAAGTAGATTTTAAATN

FIGURE 247

CGGAGCCTNTGCAGGAGGAGCTTTTCGGTCCTGGCCGNGATTTTNTGCAGGCCCCACGAGTGG
GAGGTGCTGAGCCGNTCAGGTTCTCCCTTTTGCCACTGGAATCAGGAGAATGTTGCAGAGGAA
TTGCATTCCTGGTAACAAGATAACCCAGCAAGACTCAGACTGCTAACCCAAGGATCAACTATT
AAGGCCAGACAGATGGGACCGTGTTCAGAATTCACACAAAAGCTGAAGGATTTATGGATGCGG
ATATACCTCTGGAATTGGTGTTCCATTTGCCAGTCAATTATCCTTCATGTCTACCTGGTATCT
CGATTAACTCTGAACAGTTGACCAGGGCCCAGTGTGTGACTGTGAAAGAGAATTTACTTGAGC
AAGCAGAGAGCCTTTTGTCGGAGCCTATGGTTCATGAGCTGGTTCTCTGGATTCAGCAGAATC
TCAGGCATATCCTCAGCCAACCAGAAANTGGCAGTGGCAGTGAAAAGTGTACTTTTTCAACAA
GCAC

FIGURE 248

TCGGGTTTTCGGAGCAGTTTTCGAATGGACAGCTCCGTGGAGGAGGATGAACTTATGTTAAAT
GAAGGTAAGAGTTTTGGGCATNTTATGCCCCCTTTGNTCTNTGACAGCTCTGTGTCTTGTCTT
TGGCCTNTATCCACCTCCTTCCAAGACAANTGATGATAAGACCAGCGGCTTTAAGAAATGTGA
AACCAAGTCAATTGTGTCATCGTCCATCAGTGCTTTTACATTGCCTGTGATCAAAATTAATAA
CTGTGTTATTGATGAGCCCAGTATAGATAACATCACTGAAGATGCTGACAACCTCAAAAGTAG
GTCAAGGAATTTGTCAATGGATTCCCTTGTGGTTCCTTTGCCCAACACCAGTGAATCCTTCCA
GCCCGTCAGCACAGTGNTACCAAGGAATAATTCCATTGGGGAGTCGTTGTCGAGTCAGTACAA
GTCATCTATGGCTCTCGGACCTGGGGNTGGACAGCTCTTGTCTCCTGGGGCTGCCAGAAGACA
GTTTGGGTCCAATACATCCTTGCATTTGCTCTCGTC

FIGURE 249

TCCTTACAAGGNCCGTGTAACATGACACTGTTAATGATTGCATTTGGCTTGCTGTGGGGGCAT
TTNTTGCGGATCAAACCCACGCAGAGNGTTTTCATTTTCCAAGTGTCTGTCCTTGTCAAGCAC
ACCCCTTGTGTCCAGGTTCCTCATGGGCAGTGCTCGGGGTGACAAAGAAGGCGACATTGANTA
CAGCACCGTGCTCCTCGGCATGCTGGTGACGCAGGACGTGCAGCTCGGGCTCTTCATGGCCGT
CATGCCGACTNTCATACAGGCGGGCGCCAGTGCATCTTCTAGCATTGTCGTGGAAGTTNTCCG
AATCCTGGTTTTGATTGGTCAGATTCTTTTTTCACTAGCGGCGGTTTTTCTTTTATGTCTTGT
TATAAAGAAGTATCTCATTGGACCCTATTATCGGAAGCTGCACATGGAAAGCAAGGGGAACAA
AGAAATCCTGATCTTGGGAATATCTGCCTTTATCTTCTTAATGTTAACGGTCACGGAGCTGCT
GGANGTNTCCATGGAGCTGGGCTGTTTCCTGGCTGGAGCGCTNGTCTCCTNTCAGGGCCCCGT
GGTCACCGAGGAGATCGCCACCTCCATCGAACCCATCCGCGANTTCCTGGC

FIGURE 250

CAACTTACCTGAAATGCGCTATTGAATGCACGNGNGGAAAATCCTTGGGTTCCAGGATGACAC
CTANTANTGCAGTTTGATTGGCAGAATNGTCGATACGATGGCTGGCAAATNTCCTGGTCCCTT
TCCCAANTGTGACTGGNGATTCAATGAGTTTCCCAACCCAGTTGCCCATGNTCTCCATGTTAC
TTGTGTGGAGCTCATGGCCTTGGCAGTTTCAGGCAAAGAAGTTGGGAATGCCCTTCTAAATGT
TGTCCTAAAAAGTCNGCCTTTAGTGCCAAGAGAGAACATTGCAGCATGGATGAATGCAATTGG
TTTGATCATCACTGCCCTACCAGAGCCATATTGGATTGTTCTTCATGATCGAATTGTGAGTGT
CATCAGCAGCCCCAGNTTGACGTCTGAAACAGAGTGGGTTGGNTATCCATTCCGCCTCTTTGA
TTTCANTGCCTGTCATCAGTCCTACTCTGAGATGAGTTGTAGNTATACGTTAGCTCTTGCACA
TGCTGTGTGGCACCATTTTAGCATCGGACAANTTTNTCTCATTCCAAAGTTTCTTANTGAAGT
ANTTCTTCCTATAGTGAAGACCGAATTCCAGTTGCTTTATGTATACCATCTTGTTGGAC

FIGURE 251

GAAGGGCATTTTCAGGGAGCAGAATGACAAGACNTATTGTCAACCTTGCTTCAATAAGCTCTT
CCCACTGTAATGCCAANTGATCCATAGCCTNTTCAGATTCCCTTATAAAATTTAAACCAAGAG
AGGAGAGGAAAGGGTAAATTTTCTGTTACTGACCTTCTGCTTAATAGTCTTATAGAAAAAGGA
AAGGTGATGAGCAAATAAAGGAACTTTTAGACTTTACATGACTAGGCTGATAATCTTATTTTT
TAGGCTTCTATACAGTTAATTCTATAAATTCTCTTTCTCCCTCTCTTNTCCAATCAAGCACTT
GGAGTTAGATCTAGGTCCTTCTATCTCGTCCCTCTACAGATGTATTTTCCACTTGCATAATTC
ATGCCAACANTGGTTTTCTTAGGTTTCTCCATTTTCACCTCTAGTGATGGCCCTACTCATATC
TTCTCTAATTTGGTCCTGATACTTGTTTCTTTTCACGTTTTCCCATTTCCCTGTGGCTCACTG
TCTTACAATCACTGCTGTGGAATCATGATACCACTTTTAGCTCTTTGCATCTTCCTTCAGTGT
ATTTTTGTTTTTCAAGAGGAAGTAGATTTTAACTG

FIGURE 252

ATTTGTTTGTATAATATAATACATATAGATAGAGGGGCGATAATATANTGGTAGACAAAGAAT
GCAGGAAATGCCCTTATTCATCACACCACCAAGCAGGCCTCACCCTAAAGACCCAGCAAAAGT
AACAAAAGCACATTTGGAAACCCAGGAAGCCAGTAAAAGTAAATCTAAAGGCTGACAGGGTGT
ACATTATTATGTATGTGCAATATAAATCAAATTCAAAGCTGTTTTCTCTTAAATTTTGATANT
TATAGAGACAGGANTTGCCATGGGGAATTTCTTTCCCCTTACTATATAATTTTATTACTAGAA
GGAAAAGTAATAGCAATGATAATAATGAACAGACTTNGTGTCTTTATTACATTTGCTTTCCTA
GTTACCTTTAGANTGTCACTTCTGAGTTCTTTCTCTGACATGCTTTTCTTTTCTCGTGAAGCG
TCTTACATTCTGAC

FIGURE 253

AATTTNTATNTACATTTGTGATAATATAGNTAGTGCGTAAGAATATTTCCCCAAGGTCAGTTA
AGCAAGATTTTCTTATGATCATCATTGCCATGAACTTTCAAACATAGCGATNTTGTGAAAACA
GTGCCTGTTAATTTACAATGTTTACCTTGAACAGTTGTCAAGTGTGATTTTTATAAGGAGTTG
GTATGTTTNTAAGCAGTTATNTACTTGATCTTTTTAATANTGGGGTTAAGGGAAACCTGCTTA
CAGCATCACCTATTTTTCATTCAAATGGCACATAATNGNGCATGTGTAACAGTTGTGTACCTT
TGTGGGGTTNTTTTGTTNTTTGNTTTTCTTTTTGAGACAGGGTTTCGTTCTGTTGCCCAAGNT
GGAGTACAGTGGNTCGATCTCANTGCAACCTCCACCCCCCAGGCTCAAGTGATTCTTTCACCT
CGGCCTCCTGAGTATCCGGG

FIGURE 254

CAGCGAATGTTGGGGAACNTGATTCGGCCTCCATATGAAAGGCCAGAGCTCCCCACATGTCTC
TATGTAATTGGGCTGACTGGCATCAGTGGCTCTGGGAAGAGCTCAATAGCTCAGCGACTGAAG
GGCCTGGGGGCGTTTGTCATTGACAGTGACCACCTGGGTCATCGGGCCTATGCCCCAGGTGGC
CNTGCCTACCAGCCTGTGGTGGAGGCCTTTGGAACAGATATTNTCCATAAAGATGGCATCATC
AACAGGAAGGTCCTAGGCAGCCGGGTGTTTGGGAATAAGAAGCAGCTGAAGNTACTCACGGAC
ATTATGTGGCCAATTATCGCAAAGNTNGCCCGAGAGGAGATNGATCGGGCTGTGGCTGAGGGA
AAGCGTGTGTGTGTGATTGATNCCNCTGTGTTGCTTGAAGCCGGNTGGCAGAACCTGGTCCAT
GAGGTNTGGACTGCTGTCATCCCAGAGACTGAGGNTGTAAGACGCATTGTGGAGAG

FIGURE 255

CATTATCAACCCAGCGCCACTCAAACAGGTGGACAATANCAGTTCGTCCATATTGAGTATGTG
GGTCATATTGGGCCTCTCTTTTCTCGAGAGATACCCCAGCGGCCGCAAGGGGTTCGGGGTGAT
AATAGATCAATGTGTTGGAAGTGATGGGGATGGAGAGGCGAGTCCCACTGGCGATCCGCAGCA
GGATGCCCATCAGAGAGAAGCTGGGGCTTTCCAGGACAGCATAGAAAGGCTCCACCCGGGCTG
GATGCTCCAGGACCATCCCTTCATTCTTAAAATGGGCAACGAGAAACCAGGAGACGTCCACCT
CACCTTGGAGGGAGATGAAGTGGGGGAGGTGGATTTCGGCGACAGCCTCCTCTGGCTCTGCAG
TGACATCAAACAAGGGGCCGCCCACCAGCCACTGTTCATGGTGCTGCAGGTCCAGGGCCAGGT
GCTGACTCCAGGAACCAAACGCAATCGTCACTGTGACCTCATCCCTTACCAGGAAGCCGAGGC
CTGTGGCTGACCACAGATACCAGCCAGCAGTGGGGAACCAAACGCTGTATCTGTTTGTGCTCT
TATCAATCAACTCAACATCCACATTTCCTTCAGGCCCCAGAAACTGACGATTTTTATAATCTT
CTTCGATCTCAAAACAGACTTTAGAAGCATAAGAGGAAACTATTTGATTCTCTTCTGAGCAAA
TGTCTCCTGAATCTTGTCCCTCTGAAGATTCCTGCTCTTCTGATACACTGGGAATGTCCCCCC
CAGATAGTTGACACTCAGGAACAGCACGGAACAATAATGGCTCTGCCTCTGTCTCATCATCTT
CTTGGAAAAAATGTGAGCGGACGCGTGGGTCGAGGTCGAGGGATCTCTAGAGGATCCGGCCAG
TGTGGCCTATCGATAGCTTGGAGTTGATTGT

FIGURE 256

TGGGGATCCTTGGACCTTGGACCCAGGNGTCCGTGGACGCTTGGTAGAAAGATGGCGGAGCAA
GAGCAAGGAAAAATCCCTNTGGTTCCAGAAAATCTCCTGAAAAAGAGGAAGGTTTATCAAGCC
CTCAAAGCCACCCAGGCAAAGCAGGCACTTTTGGCAAAGAAGGAGCAGAAGAAAGGAAAAGGG
NTCAGGTTTAAGCGANTGGAATCATTCCTACATGATTCCTGGCGGCAGAAACGTGACAAGGTG
CGTCTCAGACGACTAGAAGTGAAACCTCATGCCTTGGAATTGCCAGATAAACATTCCTTGGCC
TTTGTTGTACGCATCGAAAGGATTGATGGCGTGAGTTTANTGGTGCAGAGAACCATTGCAAGA
CTTNGCCTAAAGAAAATTTTTAGTGGTGTCTTTGTAAAAGTCACCCCCCAGAATCTAAAAATG
CTGNGTATAGTGGAACCTTATGTGACCTGGGGATTTCCAAATNTGAAGTNTGTCCGNGAANTC
ATTTTGAAACGTGG

FIGURE 257

TGGCCAGAATGTGAATGTATTGAATGGAGTGAGAGAAGAAATGNTGTGGCATCTNTTGTNGCA
GGTATATTGTTTTTTACNGGCTGGTGGATAATGATTGATGCAGCTGTGGTGTATCCTAAGCCA
GAACAGTTGAACCATGCCTTTCACACATGTGGTGTATTTTCCACANTGGCTTTCTTCATGATA
AATGNTGTATCCAATGCTCAGGTGAGAGGTGATAGNTATGAAAGCGGCTGTTTAGGAAGAACA
GGTGCTCGAGTTTGGNTTTTCATTGGNTTCATGTTGATGTTTGGGTCAC

FIGURE 258

ATCATATGGGCACAAATNTGGTGTCCTTTATGGNGAAAACCTCAAGTAAAAGTTTTATTCNTG
CCTTTGAAAATGGTTCCAAAAGTAGACCCTGTCCCCACACAGGTCAAGACNACAGAGAAGGCT
TTGTAGAAATGTGTCACCTATGTACACCTGNTACTTACACATTTCCTCTTTTGGAAAAAATGAG
NTANTTAGAATNACAAGAAAATTAAGACATACTGGCCTGGTGCCAGCAGATGGCTTTTCTATA
GACAAACTAGGTTAGTGTGGAAGATATNGGTTAAAATAAACTATGCTGTTTTATTTATCTTCC
CAACCTGATTGGCAGNTAGACTTTTTTAGGGTCTCATTTAATGGCCCTGTTTTTTTCATTATT
ATATTTAATGNTAGGGCAGGATTTNGTATGCAAGCTCTTGTTTNTCAGGNTGCCTGCAGAAGA
AGTCGCTATAAATTATCTGTTGTCTACATGGTACAAGGCCCATTGANTCATCTGATGCTTGTT
TTGTTAATTTCTTTAATATTTTTATCACGGGGCAGTGGGAG

FIGURE 259

AATGGCGGTGTNTACAGTGTTCTGGANTTNGTCGNTGATGCTTGCTCTGTCAAGGCACAGCCT
ATTGTCTCCTTTGCTCAGTGTGACATCATTCAGACGCTTTTACAGAGGTGACAGCCCAACAGA
TTCCCAAAAGGACATGATTGAAATCCCTTTGCCTCCATGGCAGGAGAGAANTGATGAATCCAT
NGAAACCAAAAGAGCCCGCCTGNTCTATGAGAGCAGAAAGAGGGGAATNTTGGAAAAGTGCCA
GGTAGTGGAGTAAAAAAGGNGACAGTTTATTTTTTTATTCTATGTGCACANTTACAGTATACA
TATATATTTATATCACAATTTACGAAACCAAAAAGTTGAGTTTCCAATGGAACCCTTGTTTTT
TAATAATNGACTTTTTAAATGTGATCAAGACTATAATATTGTACAGTTATTATAGGGCTTTTG
GGGAAGGGGAGGATAGCGAGAAGATGCTCTGGGGGTTTTGTTTTTGCTTTTCCTTCAGGGTTT
TATTTTTGANTGTTTTGTTTTCTTGTTGGCC

FIGURE 260

TGGATTTATANTTTTCTTCTATGTAGTTACTATAAAAGTGTGCTGGATTTGACCAATCCTTAC
CCCCANTATAAAGAGAACCCGTGATGACTTTAGTTTAAAAATTGTGGAAATTGTGGAGCAATT
TTTCTCACAATGTGAGAAAAATTNTAAACCATATTAGATAATGTGGAAGTCATATTGTCTATC
ATATATACTGCCATTTAAAAATAGGTTTTTAAAANTTAGNTAAGTCTTAAGTAATTTGCCGTT
GNTAATAATTTTATCTCCTTGAGTCGGTTGTTGGGGAGAGATGTTATATTCAATAATTTTTAG
TTATTTTGTAATGCAGAGTGTTTATTCATTTCACAGTTNTGCAATGGATGTAGTANTTTGGGA
TTGCCCTGTCCAGAAAANTTTCAGGTACACACCTTTAAAGGNAAATGTTTNTATNTCAGATGA
AACATGTAATTTGGGATGGTTCTTCCTTTGTCANTTAAAGGNAGNTAGGAAAAGTCTCTTACC
CACTTTAAACATGAG

FIGURE 261

TCTGTGGTCAACGGGGTCATCTTTAAATGNTTGGCCGTGNTTGCCCTGTCATCCCACNTGAGA
ACCATGCTCACCGACCCTGGGGCAGTACCCAAAGGAAANGNTACGAAAGAATACATGGAGAGC
TTGCAGCTGAAGCCCGGGGAANTCATTTACAAGTGCCCCAAGTGNTGCTGTATTAAACCCGAG
NGGGCCCACCANTGCAGTATTTGCAAAAGATGTATTNGGAAAATGGATCATCANTGCCCGTGG
GTGAACAATTGTGTAGGAGAAAAGAATCAAAGATTTTTTGTGNTCTTCANTATGTATATAGCT
CTGTCTTCAGTCCATGNTCTGATCCTTTGTGGATTTCAGTTCATNTCCTGTGTCCGAGGGCAG
TNGANTGAATGCAGTGATTTTTCACCTCC

FIGURE 262

CATTCTTGAACCACTTAATCCTCTNTTGACAACANTNGTAGAACAGAATCCTGAAGATATGGG
NGACCTATACCTAGATGTTGCTGAAGCTTTTCTGGATGTTGGTGAATATAATTCTGCACTTCC
CCTCCTCAGTGCTCTTGTTTGCTCTGAAAGATACAACCTTGCAGTAGTTTGGCTTNGTCATGC
AGAATGTTTAAAGGCCTTAGGNTATATGGAGCGAGCTGCTGAAAGCTATGGCAAGGTGGTTGA
TCTGGCCCCANTCCATTTGGATGCAAGGATTTCACTTTCTACCCTTCAGCAGCAGCTGGGCCA
GCCTGAGAAAGCTNTGGAAGCTCTGGAACCAATGTATGATCCAGATACTTTAGCACAGGATGC
AAATGCTGCACAGCAGGAANTGAAGTTATTGNTTCATCGTTCTACTCTGTTGTTTTCACAAGG
CAAAATGTATGGTTATGTGGATACCTTACTTACTATGTTAGCCATGCTTTTAAAGGTAGCAAT
GAATCGAGC

FIGURE 263

TTGAGACCTGGATGAACAAATTTATATCCTTTCCTTNGAGGAAGAAGCACTCCAGAGACGANT
AAATGGGNTGTCTTCATCGGTGGAATACAACATAATGGAGTTGGAACAGAACTTGAAAATGTA
AAGACTCTTAAGACAAAATTAGAGAGGCGAAAAAAGGCTTCAGCATGGGAAAGAAATTTGGTG
TATCCCGCTGTTATGGTTCTCCTTCTTATTGAGACATCCATCTCGGTCCTCTTGGTGGCTTGT
AATATTCTTTGCCTATTGGTTGATGAAACAGCAATGCCAAAAGGAACAAGGGGGCCTGGAATA
GGAAATGCCTCTCTTTCTACGTTTGGTTTTGTGGGAGCTGCGCTTGAAATCATTTTGATTTTC
TATCTTATGGTGTCCTCTGTTGTCGGCTTCTATAGCCTTCGATTTTTTGGAAACTTTACTCCC
AAGAAAGATGACACAACTATGACAAAGATCATTGGAAATTGTGTGTCCATCTTGGTTTTGAGC
TCTGCTCTGCCTGTGATGTCGAGAACACTGGGAATCACTAGATTTGATCTACTTGGCGACTTT
GGAAGGTTTAATTGGCTGGGAAATTTCTATATTGTATTATCCTACAATTTGCTTTTTGCTATT
GTGACAACATTGTGTCTGGT

FIGURE 264

TTTTTTTGGTAGAGATGGGGTTTCGCCATGTTGCCCAAGCTGTTCTTGAACTCCCGGGCTCAA
GTGATCCGCCTCCCTNGGCCTCCCAGAGTGCTGGGATTACAGNCACGGACCACCATGCCCAGC
CTCCACATCTTTTTTTGCACTGTGTATACTCTTNTGAGACATGCCAACTTCCTCCAGGTCAAG
AAAGGGGTATATAGCTCTCAGCTTCACTCTTTCAGGGCTGATGTCGCCTTTGCCTTTTCTCAC
TTCACTGACCTGTCTATTCCTACAACTGTCTCTTTCTAGAGAAGCCTCAATGATCAGGATTGA
CAGGCCACACTCTCCCCCACCATTTTTTTCTCCTCCTTCAAGCCTCTTGTCTGTTTCACCCTC
TTCCACCTTGGAGGCTGAGGTCTTATTTGACTCTTCACCTGAATTGACCTTCTTCCTTCCCAC

FIGURE 265

TGAGATCTTTTTCTCTAATTNTCAGAAGTGTTTCAATGNTATTAATTCATTATTTCCTCCTCT
CTGNTTTTTTTTTAATTCCCTGTCTGGGGAATCCTGTTATCCTGATATGAGCACTCTACTTCT
ATTCTCCATAGCACTTAGCTCCTTTAAAAATATTCTCTTTGTTCTCTACTTCTGCCTTCTGGG
AGAGTTTCTCAG

FIGURE 266

TTTTTTTTTCAAGTCTTGATTTGTGGCTTACCTCAAGTTACCATTTTTCAGTCAAGTCTGTTT
GTTTGCTTCTTCAGAAATGTTTTTTACAATNTCAAGAAAAAATATGTCCCAGAAATTGAGTTT
ANTGTTGCTTGTATTTGGANTCATTTGGGGATTGATGTTANTGCACTATACTTTTCAACAACC
AAGACATCAAAGCAGTGTCAAGTTACGTGAGCAAATACTAGANTTAAGCAAAAGATATGTTAA
AGCTNTAGCAGAGGAAAATAAGAACACAGTGGATGTCGAGAACGGTGCT

FIGURE 267

GGGCCCAGATTGCGAAATTGAGGCNCCAAGGCGGCCGAGACGGACTGAAGCATTTCAAGGNTC
CGGNGGGTTCCCATGATTTGAACGGAGTCGTTTCCCCTAATGGGTGTTTTGACCCCCATCCCG
GTGCTNANGTGGTTTTTCCCCATNATCGGCCAACATGGGCATTTGAAATCCACAGGNGTCATT
GGGANTTNGCGGGCCCCTAATTTGTTTCAGACAGGCCGGGAGGGCAGTNTGGCCAGAAGGATT
CTTAAGTAACTGACCCAGCCCTTTGCCCCCACCCTTGGGGTACCGAGACATGGGTAGGGATTA
GAGGCAAGAGTGGAGAGTCAGACCATCCAGGAACCACATNTTTGGACCTTCAGAAGGAGGACA
ACATGGCCTTTGGAAAGCCTGCCAAGTACTGGAAGTTGGACCCTGNTCAGGTNTATGCTAGCG
GGCCCAANGCATGGGACACGGCTNTGCANGACGCCTNTGAGGAGTACAAGCACCGCATGCACA
ATNTNTGCTGTGACAAATNCCANTNGCANGTGGCATTGGCCCTGAATCTGATGCGNTACAACA
ACAGCACCAANTGGAATATGGTGACGCTCTGCTTCTTCTGCCTGCTNTACGGGAAGTACGTCA
GCGTTGGGGCCTTNGTGAAGACCTGGCTGCCCTTCATCCTTCTCCTGGGCATCATCAGCGGCC
GCCGTAA

FIGURE 268

GAATCTGTTTCCAAAAAAAAAAAGCTTTAAGAAGTCTTTAGATTTACAGNTAAGCATATTCTAA
ATACTATGTGATGAATTATTTCTCTTATGTTAAAAAAAATATTAATTTGGACCCAANTATGAC
TGTGGGTATTCTGCCCAGGGAAGAAGAGCTAGGAGGTTTAAACCTTACCTTGGANTTGCTGCT
TTGTTTTCTATGCCTTCTTGACAGAAGGATTTATTTCACTTCCGAAATATTAGCCATAATGCCC

FIGURE 269

CACTAGGAAAAATTGAAATNCTATTGGAAATTNTTTTGGCCACAAAGGTAAATAGGTNTACCA
GGGGAAACAGGCATCAAGAAAATTGCCCCAATTTTTAAAACAATAGGGTTATTTGAGTAGTTG
AGTTTAAGAAATGAAAACCACAAATTTTGGTGGAACTTAAACACCACAGTCTATTTGTGTGTA
ATTTCTCAGGNTTTATTATAGTTCATGATAAAATCAATTTTCCATGTCTANTTTGTTTTTCTT
CAACAAGTGATCTATCTTTTACAAAAGGGAATATTTTGCTGGAGAAATGCTCATTGTTTCCCT
TCTGTATGTCTTTGAGGGTAATGCTAAAAGCAAGCTCAAATTTCAAAATATGTTATTTTTAAA
ATATTTTATATAGGATTTGTTAAANTTATAGTTTTCAAGGATTGTCTTTTGTTTCTTTGGATT
CTGATTAAGTGATTTTTAATGTATTCCTTTAAAAATATTTATTGGCACATTGTATTTGTACAT
ATTGATGGGATAAAATTGATGCTTCTGTACATATATATTTGGCATAATCATCAAATTTGGGTA
TTTAGCTTATTCATCACCTCATTCATTTATCATTTCTTTATGGTGAGAACATTCAAAAGTCTC
TCTTCCAGCTATTTTATAATATATTATAC

FIGURE 270

TTCGGAAGAAGCACCTCAGAGGGATTAAGCTCCTGAGAATGTTACCTGCANTATACCTGATGG
CGTGCCAATAGATATCACAGTGAAGTTGATGGTCTTCCCTTGNACATNTCAACATTNTTGAAC
CACTTAATCCTCTNTTGACAACACTAGTAGAACAGAATCCTGAAGATATGGGAGACCTATACC
TAGATGTTGCTGAAGCTTTTCTGGATGTTGGTGAATATAATTCTGCACTTCCCCTCCTCAGTG
CTCTTGTTTGCTCTGAAAGATACAACCTTGCAGTAGTTTGGCTTCGTCATGCAGAATGTTTAA
AGGCCTTAGGCTATATGGAGCGAGCTGCTGAAAGCTATGGCAAGGTGGTTGATCTGGCCCCAN
TCCATTTGGATGCAAGGATTTCACTTTCTACCCTTCAGCAGCAGCTGGGCCAGCCTGAGAAAG
CTCTGGAAGCTCTGGAACCAATGTATGATCCAGATACTTTAGCACAGGATGCAAATGCTGCAC
AGCAGGAANTGAAGTTATTGCTTCATCGTTCTACTCTGTTGTTTTCACAAGGCAAAATGTATG
GTTATGTGGATACCTTACTTACTATGTTAGCCATGCTTTTAAAGGTAGCAATGAATCGAGC

FIGURE 271

TGGTTTTTGCCCCATAAATTCCCTCAGCTTGAGCAGTTTGTTAAGGAATGAGGTTACAGATTC
AGGAATTNTAGGNCCTCAACCTNTAGANTTTGTCCCAAATGTTCTCCGACATGCAGTAGATGG
GAGACAAGAGGAGATTCCTGTGGTCATCGCTGCATNTGAAGACAGGCTTGGGGGGGCCATTGC
AGCTATAAACAGCATTCAGCACAACACTCGNTCCAATGTGATTTTCTACATTGTTACTCTCAA
CAATACAGCAGACCATNTCCGGTCCTGGNTCAACAGTGATTCCCTGAAAAGCATCAGATACAA
AATTGTCAATTTTGACCCTAAACTTTTGGAAGGAAAAGTAAAGGAGGATCCTGACCAGGGGGA
ATCCATGAAACCTTTAACCTTTGCAAGGTTCTACTTGCCAATTCTGGTTCCCAGCGCAAAGAA
GGCCATATACATGGATGATGATGTAATTGTGCAAGGTGATATTCTTGCCCTTTACAATACAGC
ACTGAAGCCAGGACATGCAGCTGCATTTTCAGAAGATTGTGATTCAGCCTCTACTAAAGTTGT
CATCCGTGGAGCAGGAAA

FIGURE 272

CCGGAAACCATGAGGTAATGCCNCAATGGCATATTGTAAATGTCATTTTAAACATTGGTAGGC
CTTGGACATGATGCTGNATTACNTCTCTTTAAAATGACACCCTTCCTTCGCCTGTTGGTGCTG
GCCCTTGGGGAGCTGGAGCCCAGCATGCTGGGGAGTGCGGTCAGCTCCACACAGTAGTCCCCA
CGTGGCCCACTCCCGGGCCCAGGCTGCTTTCCGTGTCTTCAGTTCTGTCCAAGCCATCAGCTC
CTTGGGACTGATGAACAGAGTCAGAAGCCCAAAGGAATTGCACTGTGGCAGCATCAGACGTAC
TCGTCATAAGTGAGAGGCGTGTGTTGACTGATTGACCCAGCGCTTTGGAAATAAATGGCAGTG
CTTTGTTCACTTAAAGGGACCAAGCTAAATTTGTATTGGTTCATGTAGTGAAGTCAAACTGTT
ATTCAGAGATGTTTAATGCATATTTAACTTATTTAATGTATTTCATCTCATGTTTTCTTATTG
TCACAAGAGTACAGTTAATGCTGCGTGCTGCTGAACTCTGTTGGGTGAACTGGTATTGCTGCT
GGAGGGCTGTGGGCTCCTCTGTCTCTGGAGAGTCTGGTCATGTGGAGGG

FIGURE 273

TGAAGTTGAATTGAATGATATGAGGNTTTTCTTTCCCAAGGTCNACCAGGACCAAGATTNTTT
TATAGTTATAAGCCTTGAAAGAAATTCTTGCAAGGTGTTGGACNCTTACTNAAGCAGAGAAGA
TGTCCTTTGAAACTCAGAAACGAACCTTGGTACAGAAAATCAGTATTTAAGGCCCAGAACTTA
TTGAAAGCGCAATGTACTTCTACCGTGCCACGGGGGATCCCACCNTCCTAGAACTCGGAAGAG
ATGCTGTGGAATCCATTGAAAAAATCAGCAAGGTGGAGTGCGGATTTGCAACAATCAAAGATC
TGCGAGACCACAAGCTGGACAACCGCATGGAGTCGTTCTTCCTGGCCGAGACTGTGAAATACC
TCTACCTCCTGTTTGACCCAACCAACTTCATCCACAACAATGGGTCCACCTTCGACGCGGTGA
TCACCCCCTATGGGGAGTGCATCCTGGGGGCTGGGGGGTACATCTTCAACACAGAAGCTCACC
CCATCGACCCTGCCGCCCTGCACTGCTGCCAGAGGCTGAAGGAAGAGCAGTGGGAGGTGGAGG
ACTTGATGAGGGAATTCTACTCTCTCAAACGGAGCAGGTCGAAATTTCAGAAAAACACTGTTA
GTTCGGG

FIGURE 274

TATGGGCATAGAAAACCCTGGAAAGNCCCATCCACCATTATATATAGAGTGATTGTCTNTGCT
TGNTGAGCTAACAGGGGTGTCAAGCTTCCATTTTGGTATCTACTTCTAAATACACTCAGACCA
GGAGAAATTTGGACTAATTTTCAAACTACAGACACTTTCTAATCATGATGCATTTCAAAAGTG
GACTCGAATTAACTGAGTTGCAAAACATGACAGTGCCCGAGGATGATAACATTAGCAATGACT
CCAATGATTTCACCGAAGTAGAAAATGGTCAGATAAATAGCAAGTTTATTTCTGATCGTGAAA
GTAGAAGAAGTCTCACAAACAGCCATTTGGAAAAAAAGAAGTGTGATGAGTATATTCCAGGTA
CAACCTCCTTAGGCATGTCTGTTTTTAACCTAAGCAACGCCATTATGGGCAGTGGGATTTTGG
GACTCGCCTTTGCCCTGGCAAACACTGGAATCCTACTTTTTCTGGTACTTTTGACTTCAGTGA
CATTGCTGTCTATATATTCAATAAACCTCCTATTGATCTGTTCAAAAGAAACAGGCTGCATGG
TGTATGAAAAGCTGGGGGAACAAGTCTTTGGCACCACAGGGAAGTTCGTAATCTTTGGAGCCA
CCTCTCTACAGAACACTGGAGCAATGCTGAGCTACCTCTTCATCGTAAAAAATGAACTACCCT
CTGC

FIGURE 275

TGGGACACGGGTTACCCCAAGNGCAGCGCTGGCAAGGCCTTCATGATNTCGGTGTGCTCTACG
TGACCAATTCCCACCTGGNTGGGGCAAGGTCTACTTCGCCTATTTTACCAACACGTCCAGTTA
GAGTACACGNACGTGCCCTTCCACAACCAGTATTCCCACATCTCGATGCTGGATTACAACCCC
CGGGAGCGCGCCCTCTATACCTGGAACAACGGCCACCAGGTGCTCTACAATGTCACCCTGTTT
CACGTCATCAGCACCTCTGGGGACCCCTGAGCCAATGCTGTGGCTCGGGCTGCTGCCTGGGGG
GCCTCCGGGGGCTGGGGGCCCTTTTCATTCTGCCTGTGTCCCTCAAGGGTGATCTCTCTGTCT
CTGTCACGCCCTTTCTCCCCGCCTTTTTGCTGGGCTTTTGTTCTCTGCCTATGTATTTCTGTC
TATTTTTTCAATTTCCCCTCTTCTCCTTTATTGATCTCTGCTTTTAATACACCACTTCTTTCT
TTCTGCCTTTTTATGGATGTCTTTTTCTTTTTATGGCTCTGGTTCTCCAGTTCTTTCCGTCTC
TGCCTCTCTCTGTCTCTCTCTCTCTGTCCTTCCACCCCTCCCTCCTTGCCTCCC

FIGURE 276

CGAANGCGTGGGTGTGCATCCGGGTGTNTGAAGGCTGTGCCCGTTTTGTTTCTTGGCTAAAAT
CGGGGGANTNAGGCGGGCCGGCNCGGCGCGACACCGGGCTCCGGAACCACTGCACGACGGGGN
TGGACTGACCTGAAAAAAATGTCTGGATTTCTAGAGGGCTTGAGATGCTCAGAATGCATTGAC
TGGGGGGAAAAGCGCAATACTATTGCTTCCATTGCTGCTGGTGTACTATTTTTTACAGGCTGG
TGGATTATCATAGATGCAGCTGTTATTTATCCCACCATGAAAGATTTCAACCACTCATACCAT
GCCTGTGGTGTTATAGCAACCATAGCCTTCCTAATGATTAATGCAGTATCGAATGGACAAGTC
CGAGGTGATAGTTACAGTGAAGGTTGTCTGGGTCAAACAGGTGCTCGCATTTGGCTTTTCGTT
GGTTTCATGTTGGCCTTTGGATCTCTGATTGCATCTATGTGGATTCTTTTTGGAGGTTATGTT
GCTAAAGAAAAAGACATAGTATACCCTGGAATTGCTGTATTTTTCCAGAATGCCTTCATCTTT
AAT

FIGURE 277

AGTTTCCTTTAAATTGGGGTNGGGGTGTTAAGCNCTGAAAATATCTTTCNTGATTACTTTACC
ATGTGGACATATGGGATAAATACTGTATTTCAGATTTACATAAAAGTAGATTAGTAATGCNCA
GCTTTCAGAATAAAAACTGATAAAAAAGACCAAGCACTATCAACTTTGGACAGTAATTTCTTA
GGTGTTAAACAAGTTTTCTGAATACAATCTGGATGCAAAACGGCCTGATTTGATGAATTCATA
ATTTTCTTCTGNANACTTTCATTTTATTAAATATTTTATTACTTGGTTAAACNCNAGAATTAT
CTATGTAAACTTCATGGGNTTTTTTGTTGAAAGTTAGATGTTCAGTAACTAATTTCCCAGTTA
TGGCCCAGAATTAAACATTTATGATCATATTTCAGAAGTCAAAATNCAAAACTGGATTATCAA
AACGGTTGGTGTGGTCNCTTTAAACTGGACTATCAGTATGGTTGCCGTGGTCACTTTAANCGG
GATTATCAGTACGGTTGGTGTGGTCACTTTGGTTTATCATCAATACAGTTGGTGTGGTCACTT
TAAACTGGATTACCNATATGGTTGGTGTGGTCGCTTTAAAGTTTGNTTTCATTTTTTTCTATT
TTTAATTNTTAC

FIGURE 278

TTGGTTTTTCTGTTCCTGNGTTAGTTTGCTGACTTAAGAGGATACAGACTTGAGGTATAATTT
GTCTTAGTCAGTTTTGTGTTGCTATAACAGAATACCTGAGACTAGGTAATTTATAAAAATAAA
GTTTATTTGGCTCATGATTNTGGAGCTGGAAAGTCNAGATTGGGCAGCCCATATGATGAGGGT
TGCACACTTNTTCNATTTATGGCAGAAAGTGGAAANGGAAGCAGGTGTGTCCAAANAGACATG
CAGGAGAGGTTGGAGTCANTGCTCTCTCAGGAANTAATTCATTCTNTAGAGAGTGAGAACTCA
CTTAACTNTTGCNAGAGGGCATTAATCTATTCACCCATGAAACNAACACCCTNCAGTAGACTC
CACCATTTAACACTGCCATATTGGGAATCAAATTTCAACATGAGTTTTGGCANGGG

FIGURE 279

CCTTTGGAAACTGGGATTAATGTATGCTCTAGATCCATTTATTAGAAATGCAAAAATACTACA
ATTTTTTGATGGATGAAAATACTCCTGTAACACAAACAGAGAACTGGAGGAACTGAAGAATAA
CTCACTCATATAGNTCTGCCTCATTCTGTGTGTGTGTGCATGTGTGTGTTANCAGAGGTATTT
TACTCAGAAAATAGGTTTCAAAGAACATTAATGACTTTCTTTTCCCTTTTANGTNTGNTTAAT
CAGTTAAACTGNTATGGGAAAAGTTTTATAGAACTATATAACCTGAATGTTGGTCTCTTTGNA
CACATNTTTTNTATGACTGC

FIGURE 280

TGTGGTCCTAATATCATAGATCACTTTANATGTGATTTGTTTCAGTTGTTGACACTTGCCTGC
ACGGACACCCACATCCTGGGCCTTTTAGTTACCCTCAACAGTGGGATGATGTGTGGCCATC
TTTCTTATNTTAANTGNGTCCTACACGGTCATCCTANGCTCCCTGAAGTTTTACAGCTTTAAA
NGGCGGCACAAAGCCCTNTNTACCTGCAGNTNCCACCTCACGGTGGTTGTANTGTTCTTTGTCCC

FIGURE 281

TGGTTCCAGGTCACCATCCTTAGCNTCAAATTCATAAAATGGTTGCTTCTACCTCCAGCCTGA
TATCCTTGTGATGGGCAGGCAGAACCAGGGCTNTAAGGAAAGGAGCCAGCACCTGTATCAAGA
AGCCAAAGCCTTCCCTGAAATCTTTAGCAGACGTCTGCTTGTGACTATTTGGCTAGAACTTTG
TGACATGGCCACTCCNTGCTGCAAGGACATTTACAGTTTTTCAGTTGGGCCCATTGCCACCCT
GAGCAAAGGGTCNATAAGGAAGAAGACGGAGAGTGGACATGTTGGGCATTCACCTGCCAGCAC
TCCATCCAGACAGCCNCANAANTGGTGGGTAAACAGAGACAGCATACATTCACTTATCAACTG
TTTAGTAAATTCCTGGCATGGGCA

FIGURE 282

AGCCCAGATCCAGGAACCATTCCTATTTCAGGATTTTGAATGCAAAACTTACCTTNTTACTCT
AAAGATGAATGTCAGGGAGAGATTTATTCAACCCTGAGATTTTTGCAGTCTCCTTCAGAGTCA
CAGAATAGATTAAGGCCTGATGATACTCAAAGGCCTGGGAAAACTGATGNCAAAGAATTTTCA
GTGCCCTGGCACCTCATTGCAGTGACTNTTGGGATCCTCTGNTTACTTCTTCTGATGATAGTC
NCAGTGTTGGTGACAAATATCTTTCAGTGNATTCNAGAAAAACATCAACGGCAGGAAATTTTA
AGAAACTGTAGTGAAAAGTACNTCATGCAAAATGNCNACTACTTAAAANAGCAGATTTTGACA
AATAAGACTTTAAAATATGACGTTNTCAAAAATAGCTTTCAGCAGAAAAAGGAACTGGATTCA
CGCCTTATACNAAAGAACAGATGTCATAGAGAAAATGAGATCATTTTTAAAGTTTTGCAAAAT
ACAGGCAAATT

FIGURE 283

AGGAATGACCTTCCTCAGGGGGCTGAGGATACCCCACAGGCCTCCTTTCTCTCCAGCTCCAGG
GTTTGACTATGCACCTATTTAGGGGCTGCTTGCTCAAGGGAGAGAGGTACAGGAGGTGGTCTG
GGAAAAACAAAATTGATCTTCCTATCAATTGTATTTTTGTTTAGCGGAATCTATACACACCCA
TTTCTTTGGATATTATTTCCAGTTACTCCAGCTAATCCAAATAATGATATTTGCCCTCAGTTA
AGAACAGATTTTATTTTTAGGAACAGAAGTCTAGTAGCAGTTTTGCTTTTTATTAACGTTTTA
AGGAACATTTACCTTAGATATCATGATTCTTGGGCATTTGCAAAATGCAGTCAATATCAAACA
GCAATGGTTGCTTGTTTTATGATCGGTCAGAATTTGTCCCTTATATTAATTTCAG

FIGURE 284

GCCCCGAGTTTCTGTCGCAGGTTGCGAGGAAAGGCCCCTAGGCTGGGTCTGGGTGCTTGGCGG
CGGCGGCTTCCTCCCCGCTNGTCCTCCCCGGGCCCAGAGGCACCTCGGCTTCAGTCATGCTGA
GCAGAGTATGGAAGCACCTGACTACGAAGTGCTATCCGTGCGAGAACAGCTATTCCACGAGAG
GATCCGCGAGTGTATTATATCAACACTTCTGTTTGCAACACTGTACATCCTCTGCCACATCTT
CCTGACCCGCTTCAAGAAGCCTGCTGAGTTCACCACAGTGGATGATGAAGATGCCACCGTCAA
CAAGATTGCGCTCGAGCTGTGCACCTTTACCCTGGCAATTGCCCTGGGTGCTGTCCTGCTCCT
GCCCTTCTCCATCATCAGCAATGAGGTGCTGCTCTCCCTGCCTCGGAACTACTACATCCAGTG
GCTCAACGGCTCCCTCATCCATGGCCTCTGGAACCTTGTTTTTCTCTTCTCCAAC

FIGURE 285

ATTTAGATTTGNATCTCTTCCCATCAATCATGAATACATAAGGTAATATTTTATAGTTGGAAA
GCATTGCTTAATATATTGAATCAATAAAAATATTGATTTCATATATTTAATTTTTATAATCTT
TACAGATTACAATACTGTGATGAGACTGTTCCTGTAACTTTTGATCCACACACAGAATTTCTT
GGTCCTCAGAAGAAAACAGAACAAGTCCAAAGAGACATTGGATTTTGGTGTCCAAGGCATCTT
AAGACTTCTGGGGGACAAGGATATAAGTTTCTGGGAATTGACCAGTGTGCGCCTCCATGCCCC
AACATGTATTTTAAAAGTGATGAGCTAGAGTTTGCAAAAAGTTTTATTGGAACAGTTTCAATA
TTTTGTCTTTGTGCAACTCTGTTCACATTCCTTACTTTTTTAATTGATGTTAGAAGATTCAGA
TACCCAGAGAGACCAATTATATATTACTCTGTCTGTTACAGCATTGTATCTCTTATGTACTTC
ATTGGATTTTTGCTAGGCGATAGCACAGCCTGCAATAAGGCAGATGAGAAGCTAGAACTTGG

FIGURE 286

CGTTAANACGAGCCTGCCAGTAAATGTAGCCATCATGTTCAGTAANGGCCTTGCAAAACAGAT
TACCCCTTCACCTTTTCACTTAATTGTCTACCTATGAATCATTAATGNTTTGGTTTGNTTTTA
ATTCTGTGATAGGTAGGAAAGGATGGAACTCCTTGGCAGACTAGTGTTANAAAGTTTTNGAAG
CAGGGTGAGTCTTGTACCTTTGNGGTCCTGTNTCACAGACACCTGTNTANTCCCTGACCCCTTT
TAAATGGTAACTTTNTGCCTGTAGGAAATCTTCCCTTTGTGCTTAGGTCTTTTTCNTCTGTGA
GCTTTAGATAAACNACCTAGTGTTTAAACTTTTTAATAAGGGATTCATTTTTTAANACATGAG
AATTCATTTCAAAANTTTGGNTTTAGNTATTTANTTTANTCTACNTGGNTCTTTTTCAGACAG
ATGTTCTCTCCTGGATTGTAAAAGTCGAATTCAAAGGATTTTTANTTGNAATANACTTAACCT
TTCTCTTGTAAGNTGCCATNTGTGTANANACAGCTTTGANTGCCTGACAAGAGGAAAATGTTT
CCC

FIGURE 287

AACTGTCTTTAATGGCCCAGTTTTACCAGGGCTTGTTGTNTAAGGACATTAACTTGTGCTCCC
CTCAGGGATGGGTTTANTACTAGCTGTCAGAAAGCTATTGGGTATCCTAATGTGTTAATAGCT
GAAACTCAGCTGTAATTTCTCCTAAATACTTCAGCATTTTGCATTCTGTACANTGTGGTGCTT
TTTCCNCCTTGTANTGTTCTAACTGTAAGCTCCTAGGGGGCAGCAATTTGGATAAATCTTTTG
GTAAGTAGTTNTCAATAAAATATCTTCCCTCCCCATACCCCTACCCGAAATNTTATANTGNTC
TTTACAAAACTTTGGTCAAGAGTAGAAATATATCCAGGCAGATGTATATGCCATACAATAGCA
AGAACAGTAAAGCCCAACTAATGATTTTGAGTTTTAAAAATAGAAGGCNATTAAAATGNACTC
AAAGTTACATTAAGAAAAGCTTTCACGGGGGTAATATTGAAACAGTCACAAAGGTTAAGAAAA
TACTGATAGCAGTTTTTGTCTATTTTAACATTGTAGTCATTTGTACTTTGAT

FIGURE 288

GGATTTTCGTAAGTAGTTTAGAGATAGTCACATTTTAAAAATTTAAGATCAAGCAAATGAAGC
TTATTTTTANGTATTCATAGTATAAAAGACCTTCAGTAAATAGGTAATANTTTTGTTTTATTC
TAGAAAACAGCTCCTTGAACACAGTGAGCTGGCTTTTCACACATTGCAGTTGTTAGTGTTTAC
TGCCCTTGCCATTTTAATTATGAGGNTAAAGATGTTTTTGACACCGCACATGTGTGTTATGGN
TTCCNTGATANGCTNTNGACAGCTNTTTGGCTGGNTTTTTNGCANAGTTNGTTTTGANAAGGT
TATCTTTGGCATTTTAACAGTGATGTCAATACAAGGTTATGCAAACCTCCGTAATCAATGGAG
CATAATAGGAGAATTTAATAATTTGCCTCAGGAAGAACTTTTACAGTGGATCAAATACAGTAC
CACATCAGATGCTGTNTTTGCAGGTGCCATGCCTACAATGGCAAGCATCAAGCTGTTTACACT
TNATCCCATTGTGAATNATCCACATTACGAAGATGCAGACTTGAGGGGTNGGACAAAAATAGT
TTATTTTACATATAGTNGAAAATNTGC

FIGURE 289

TCCCTTAATTCCATAGACCCCGAAGGGGGTTTCCCGGGTTGGAATCCATTAAATCCGGGCCAG
GGCTTGNTCCCGTGGTTTAGGATTGGGGGTTANAAATAAAAANTCAGGTNTATTTNTTACCAG
TCAGTACNATTTTTAAAGAATGTACTTGGTATATAATATATGGACTTCAGGAACTTTATTGGG
GTGGGGGGTTAATTTTGCCTTACCCTGTTCACTTTCANATGATTAGGCTTTTGCACTTTAGAA
TGAGAAACTTGTGACGTTAGTGTGTTCTTACTAGCTTTAATTTGTANGTAGCAATGAATTGTG
AATCTTAGTGCAGTGGGTTTTTTTAAAAAACTCAAAAAGCTGGGAATTAAGTGGTTTCAGTAA
TAATGNTATACCGAGGTGCTTGCATTGTATTTCATAATTTTGNTACAAACCNAAATTATTTTT
AATGAGAACAGTNTTGGGTTCANAGGTGTGATGCCAGAATGTATTTTCGTACTGTTAGGCCCT
TGGAACAGATATCGGTGCTTTTTGAAAGATGAAAGAAATGCNATGGGTGCTNTTCANGCAAGG
TTGCAAACCTACCAAGAATGCATAATAGTNTCACTTTTCCCCAATAAANAGATGNGTGTGACT
AGTTTTGGACTTTTAACCTTAATGGGGGTTGCATGTNTCCTANTGTTAATCATTGTCAGCTGC
AGTGACATGATCCACAGTNC

FIGURE 290

GACTTGGAAGAATTGGACCTAGTGGNTAGACCCAAGGNCCAAAGCCAANAATTCGTGGGGGGC
CCAGGAANCAGGAGGTCNCATGGGATTCCAGACATAAGATCAGGTTTTAACCCCCTTTGGCCC
AAATTTTGGCTGAAAATGTTGAATTATCAACTCTGAAATTAAAAAGAAAGTTTATATTAAAAC
ANTGCAATTTTCCTTAGAATTTCTGTATATATTAACATCATGAATGATAAATTCTCTTCAATG
TGCANGTCAGGTTTTTGNACTTGNATATCAAATCTATCTGTGTGTATGAAGTGTATGTTTATT
GAAATACNAGATATTTAAGAAGCTGATNTGGAAAGTTGGATTTTCATTCTAGTTCCTAATTCC
CAGAGGNTTTTTTAAAGGAAGGGAATGTNTGTGGTACNCCAGTTGTCAGCTGGGTGGNTACTG
GATCATCTTTCTTTTATCAACNAGATNAACTATCAACTTCACCAGCATCATGAACCTTGNTGC
CGTAAAAAGGAGTTCACTACTTCTGTTCNCTTTGAGTCTNTTCAAATGGATTNTGTGTCCTCC
TNTGGAGTNTGNGCCATTTANTGNTTNTGACTNTTCCNCTAAGCCAGAGAATGATGATGGAGG
AAATTATGAAATGTTCACNCGAAAATTTGTTTTTCGACCTGAACTGTTTGANGTCAC

FIGURE 291

AACCCATGGGGCCAAGTCAAAAGCCCNCAGGTTNTCCAGGCAAGGGCATGGGCATGGGGTTAG
GANCAGTGAACCTGGAAGTAATCCCAGCCCTGCNGTCATTAGTGTGTTACCTCAGGTAAAGGG
GGGGAACCCTACAGGACTGTTACAAGGATTAAATGAAGGAATTTAAGTGTGTGCATGTATNTG
GCATGTAGAAAATACAGTGTGGTGGGGAGAGAACAGATTNTAGAACCAGACTGCCTGAGTTCA
AATCCCAGTTNTGCTGCTTCCTGGCTGTGTGACCCTGGGCAAATCACTTAGCCTGTNTGGGNT
TCAGATTTCTCATCTGACAATGAAGATAATNAAATACCTATCTTTATGGTTGTAGTAAGGATT
AAATGAATTGAAATAAAGNTTTTAGATTAATACTTGATATGCTACATAGGTGTCAGCCATTGT
TAATCANTGNTGTCATTATAGNTATTATCAACATGATTATTTGCTNTAANAGGAACTCAGGCA
TTTGCAGGGTGTGGGGAACCCTGAGCTGGGTNTCCCCTGTTGGGTGTTGTGTCCCCATNATAC
CCTTAGGNCAACCCAGGTCAGGTCAGGGGGATGTGCCCTTNTTTTCCTGGNCCAGGTNTGTAA
GGCCANCAGCTTTGCCTCATACGTGNGCAGCAGGTNGTTATGG

FIGURE 292

CTAACCCCAGTTGAATTTTTGGAGCTTGTTGGATTTGCCCATTGCCAGCCCAANTATGTTGGG
GAAAAGTNTNTGAGTGTCATTTTGCNTGTTGAAGCTCTGGNTAATGTGATTATTGATCTGAGA
ATGAATCTTTNTTAGNTATTCCAAACTTAGTTATTTTTGCAGTTTTGGTANTTTTTTCCTCAT
TGGAACTCCCAAAAATCCGATTGCTTTTGCGTGTTTTTTTATTTGCCTGATAACTGATCCTTT
CCTTGACATTTATTTTAGTGGACTTTCAGTAACTGAAAGATGGAAACCCTTTTTGNACCGTGG
AAGAATTTGCAGAAGACTTTCAGTCGTTTTTGCTGGAATGATTGAGCTTACATTTTTTATTCT
TTCCGCATTCAAACTTAGAGACACTCACCTNTGGTATTTTGTAANACCTGGNTTTTCCATTTT
TGGAATTTTNTGGATGATTTGTCATANTATTTTTCTTTTAACTCTTTGGGGATTCCATACCNA
ATTAAATGACTGCCATAAAGTATATTTTACTCACAGGACAGATTACNATAGCCNTGATAGAAT
CATGGCATCCAAANGGATGCGCCATTTTTGNTTGATTTCAGAGCAGTTGGTGTTNTTTAGTNT
TNTTGCAACAGCGATTTTGGGAGCAGTTTNCCG

FIGURE 293

TCCAGGATTTTTCTCCCTGGTNTAAGGTCCTGGTTCACACCCANAGGAACCAGTTTGGTCCTG
GGCAAGCCACTGCCTATAGGATAAGGNAAGATCAAATAAATCATNTCAGGGAGAACAAGGNCC
AGCCTTCCTCCTCTATTCACTCAAACACACCACCCAAGCACCCANTTTGGCCAGACTCTGTGA
TGGTCCCTGCCCTCAAAGGACTGTTCATGGTCTAGAGATGAAAGAGCCCAGTCAACAGTTATA
CTGTGTGGTGGCGGCGGGAGGGTAATCACAGGGTATTTATGGGTACAAAAAGGAGGCACCCTG
ACCTCACCAGAAATAGCTACCCTGTGCCATAGGCTNTAGGCAGACTTTACTGACATTGAANAN
CCTTTTGCAGNCAATTANCAAAAAGACTACATGTGTAAATGTGACAGAACAGGGATTCAGAGC
CTGAATGTTTANGCCTGCTTTATCCTCATTTTGTCNCTGTGGAGGCAGAGGTGGGAAAACTAA
GTNTAGAAGCCATNTGAGTNTGGGTGGGAGCCACCTNTATATTTGTCATAAGTCTCTGATGGT
CCTTTGGTTTCTAGCTATANCTGTGTCCACTAGTGC

FIGURE 294

TTAAGGCCTTTTAAAATGGTGGAAATTTTTGGNACAATTATNCGGAAATTTTTAATTTTTAAG
GAATTTTGGAAAGTAGTTTAAAGATAGCCCNTTTTNAAAATTNTAAGATCAAGCAAATNAAGC
TTATTTTTAAGGATTCAAAGNATAAAAGCCTTCAGTAAATAGGTAAAATTTTGGTTTATTNTA
GAAAACAGNTCCTTGACACAGTGAGTGGCTTTTCACACATTGCAGTTGTTAATGGTTTACTGC
CCTTGCCATTTTTAATTATGAGGCTAAAGATGTTTTTGACACCGCACATGTGTGTTATGGCTT
CCTTGATATGCTCTCGACAGCTCTTTGGCTGGCTTTTTCGCAGAGTTCGTTTTGAGAAGGTTA
TCTTTGGCATTTTAACAGTGATGTCAATACAAGGTTATGCAAACCTCCGTAATCAATGGAGCA
TAATAGGAGAATTTAANAATTTGCCTCAGGAAAAACTTTTNCNAGTGGATCAAATNCAGTACC
ACATCAGATGCTGTCTTTGCAGGTGCCATGCCTACAATGGCAAGCATCAAGCTGTNTACACTT
CATCCCATTGTGAATCATCCACATTACGAAGATGCAGACTTNAGGCCTGGTTGCAGTANGCTT
GAAATCTGGGATGTGGAAGACCCTTCCAATGCAGNTAACCCTTCCTTANGTAGCGTCCTGNTC
GAAGACGCCAG

FIGURE 295

TCCAAAAAAAAAAATAATGGAAAACTGGAAAGAGAAAAATTGTTTCAAAAACTATAGCACACCT
GTTGTTAGATTCTTGTCTTGCCTAANGTTTTTCAATTTTANTATTTTCTACAGTTTGGACCGA
ATTCTAATTTTTNTTGACTACAAGTNTTCAAAATAATGNTTTCANTTTTTTCTTCTTTTTTCC
ATTTTTTTCCAATTTGGAGTCNCTGAAAACTAANCTGTGCTTTCATAAAGCCCTGCAAACTGA
ATCTAGACAACTTCAGAAGAAAAATNACAGCAACCTATTTACATACATAAGCCACTTTCANAC
CTGCCTACCGATGTATGGACTTCAGAGTAATGTGGNTTATAGCAATTTTCCAGGATTGNTCTT
TTGTTTGNTGNTGTTCTCCCTTCCTCCCCCTATTTTGTCTTTATGGGACATGACACTTCACAA
CCTTNTAAAAATGAGTTTTCCTAATAACTCAGGACCTACTNGTNTAGAAATNAACCATCCTAG

FIGURE 296

TTTTTTTTTCCCCTTTGGGCCAGGTCGGGGTATGATAGGTCGGGGAANAGGGGGCTTTGGAGG
CCGAGGCCGAGGCCGTGGACGAGGGAAAGGTGCCCTTGCTNGCCCTGTATTGACCAAGGAGCA
GCTGGACAACCAATTGGATGCATATATGTCGAAAACNAAAGGACACCTGGATGCTGAGTTGGA
TGCCTACATGGNGCAGACAGATNCCGAAACCAATGATTNAAGCCTGCCCATCCTNCCATGANA
GACTNTTGTTAGTCAACACATCTGTAAATAACCTTGAGATNACAGATGAGAAGAAATCTGATT
GATGCTGGATGGACCTATCACAATAGGCTGTGGACTTACTTGCCACCAGNTTGTGCATTTAGT
GTGTTCCTTTTACTTTTTGATACTGTGTTGTATGAAACCCTTTTGTCCTTTGATTTGGTTTTT
TGNTTTTGTTTTTTTANGGGGGANGGGGGTTTCCCCTCCTTTGCCCAGACTTNTCTTTGAAC
ACAAATGCATTAGCCTTGTGGNTAGAACACCCTNTTCCTACCTCTGTNTCCCC

FIGURE 297

GGTAATGGAAAACCCGCAATTACATTTGAACCAACCTAATAGATNTAAGGAAAAGCGCTTTCC
ATTCGTAGCATCAGTCTGGCCACATCCCTTGTGAGCCACTGCGCCCGGCTTGTTGGCCGTATT
TTTGGAATGCATTTGGAGCTTGGGTCAGTAGTTTTTGTTTTCATGTGATGTCACCAACATGTT
GCCTATACAGATTGAATATCCCTTATCCAAAATGCTTGCAACCAGAAGTGTTTTGGATTTTTG
GAATTTTTTTTGGATTTTGGAATATCTTCATGTAAATAATGAGATTTGTTGGGGATCAGACTC
AAGTCTAAACATGAAATTCGTTTATGTTTCATATATACTTTATACACATACCTTAAAGGCAGT
TTTATACAGTATTTTCAATGGTGTGCATGAAACAAAGTTTGTGTTCATTGATCCATCAGAAAG
CAAAGATGTCACTGTCTCAGCCACACGTGGACAATCTGGTTGGTTAGCGTCCCCATCGTT

FIGURE 298

GGCCCCGCGTGCCGACATGGGAAAGTCTCTTTCTCATTTGCCTTTGCATTCAAGCAAAGAAGA
TGCTTATGATGGAGTCACATCTGAAAACATGAGGAATGGACTGGTTAATAGTGAAGTCCATAA
TGAAGATGGAAGAAATGGAGATGTCTCTCAGTTTCCATATGTGGAATTTACAGGAAGAGATAG
TGTCACCTGCCCTACTTGTCAGGGAACAGGAAGAATTCCTAGGGGGCAAGAAAACCAACTGGG
GCATTGATTCCATATAGTGATCAGAGATTAAGGCCAAGAAGAACAAAGCTGTATGTGATGGCT
TCTGTGTTTGTCTGTCTACTCCTTTCTGGATTGGCTGTGTTTTTCCTTTTCCCTCGCTCTATC
GACGTGAAATACATTGGTGTAAAATCAGCCTATGTCAGTTATGATGTTCAGAAGCGTACAATT
TATTTAAATATCACAAACACACTAAATATAACAAACAATAACTATTACTCTGTCGAAGTTGAA
ACCGAACCCCT

FIGURE 299

GAGCGGAGCCGGCGGAGCCTCTGGAATCACCCGGGTCGCTGTTCCTGAGCAGCTGCAGAGCAT
CGAGGGCTGGAGAGGAGCACATACTGTCCATGGAGCTGGTGGTCAAGGTGGACAGGGGCGGTG
GTGATGGCGCAGTTTGACACTGAATACCAGCGCCTAGAGGCNTCCTATAGTGATTCACCCCCA
GGGAGGAGGACCTGTTGGTGCACGTCGCCGAGGGGAGCAAGTCACCTTGGCACCATATTGAAA
ACCTTGACCTCTTCTTCTCTCGAGTTTATAATCTGCACCAGAAGAATGGCTTCACATGTATGC
TCATCGGGGAGATCTTTGAGCTCATGCAGTTCCTCTTTGTGGTTGCCTTCACTACCTTCCTGG
TCAGCTGCGTGGACTATGACATCCTATTTGCCAACAAGATGGTGAACCACAGTCTTCACCCTA
CTGAACCCGTCAAGGTCACTCTGCCAGACGCCTTTTTGCC

FIGURE 300

TATGGAACAGCCTCCTTTTGACANCAGTTACGGGCTGGTGGTGGCAGGGTCTGTTCTGGTCCT
GGGAGCCATCATCGGTGACTGGGTGGACAAGAATGGTAGACTTAAAGTGGCCCAGACCTCGCT
GGTGGNACAGAATGTTTCAGTCATCCTGTGTGGAATCATCCTGATGATGGTTTTCTTACATAA
ACATGAGNTTCTGACCATGNACCATGGANGGGTTCTCACTTCCTGNTANATCCTGATCATCAC
TATTGCAAATATTGCAAATTTGGCCAGTACTGNTACTGCAATCACAATCCAAAGGGATTGGAT
TGTTGTTGTTGCAGGAGAAGACAGAAGCNAACTAGCAAATATGAATGCCNCAATACGAAGGAT
TGACCAGTTAACCAACATTTTAGCCCCCATGGCTGTTGGCCAGATTATGACATTTGGCTCCCC
AGTCATCGGCTGTGGNTTTATTTCGGG

FIGURE 301

ACCGCCTGACCGTGCTGGCTGGTGCAATGCTTGCCTTGGGACTAATGACATGCTTGTCAGTTT
TGTTTGGCTATGCCACCACAGTCATCCCCAGGGTCTATACATACTATGTTTCAACTGTATTAT
TTGCCATTTTTGGCATTAGAATGCTTCGGGAAGGCTTAAAGATGAGCCCTGATGAGGGTCAAG
AGGAACTGGAAGAAGTTCAAGCTGAATTAAAGAAGAAAGATGAAGAATTTCAACGAACCAAAC
TTTTAAATGGACCGGGAGATGTTGAAACGGGTACAAGCATAACAGTACCTCAGAAAAAGTGGT
TGCATTTTATTTCACCCATTTTTGTTCAAGCTCTTACATTAACATTCTTAGCAGAATGGGGTG
ATCGCTCTCAACTAACTACAATTGTATTGGCAGCTAGAGAGGACCCCTATGGTGTAGCCGTGG
GTGGAACTGTGGGCGAACCCCTTGC

FIGURE 302

TCGAACCCANGGGGNCCGCCGAACGCGTGGGACCATATAGAGAAATAGCATGAATATTTTTAT
TAGGAGATGTTTCAAAGACTGTATTCCAATGGTTAAAGGAAAGTCCAAAACCTCTTTAAGGAA
CACTGCAAGTTGAGCCTCTGCTGTTTTAATAGGTAGGTGACCTTGCCTGAGTCAGTCTTTTTG
AATTTCAATTTTCTAATCTTTAAAATGAGGTTTTTGGTGATCCCTCAGTTTCCTTTCAGCTCT
GGAATTTGGTGGGTAAGTTACCTTGAATGTGTATCTTTTCTTGTTAAAATTTTAAAAAACAAT
ATAGAAGGAAACAAATCCTTTTTACTCCTATTTTTTAGAAATAACCCCTAAACCTGGTAATAT
TTTGACGTGTTTTTTTCAAACTTGTCTGTGCATTTTTTAAAGGAGCTTCTGTCGTATATAGTT
ATGCCCTGCTTTTGTGTGCATGTTAAGCATTTGGTATGTTATTTTAAAGTGGAATGCCTTGAA
GAATGAATCAGTCAGACCTACTGTTAACATTTTGATGTATTTCAGACTGACTTACAATTTTTT
GGTATTTGATATTATGTATAATTATATCCTGCATTTACTTAGCATATTAAGGATTTTTTTATA
TGTAATTTTAAAGTGGAA

FIGURE 303

ATTTTTTATGTATTCATAGTATAAAAGACCTTCAGTAAATAGGTAATATTTTTGTTTTATTCT
AGAAAACAGCTCCTTGAACNCAGTAAGCTGGCTTTTCACNCATTGCCAGTGGTAAGTGTTTAC
TGCCCTTGCCATTTTAATTATGAGGCTAAAGATGTTTTTGACACCGCACATGTGTGTTATGGC
TTCCTTGATATGCTCTCGACAGCTCTTTGGCTGGCTTTTTCGCAGAGTTCGTTTTGAGAAGGT
TATCTTTGGCATTTTAACAGTGATGTCAATACAAGGTTATGCAAACCTCCGTAATCAATGGAG
CATAATAGGAGAATTTAATAATTTGCCTCAGGAAGAACTTTTACAGTGGATCAAATACAGTAC
CACATCAGATGCTGTCTTTGCAGGTGCCATGCCTACAATGGCAAGCATCAAGCTGTCTACACT
TCA

FIGURE 304

ATGAAATCCTGCTTTCTTTTCCTCAGAACTACTATATTCAGTGGCTAAATGGCTCCCTGATTC
ATGGTTGTGGAATCTGGNTTCCCTTTTTTCCAACCTTTGGTTAATTGGAATTGATGCCCTTTG
CCTTTTTCTTTCTGGAATCAGAAGGCTTTGCTGGCCTGAAAAAGGGAATCCGAGCCCGCATTT
TAGAGACTTTGGTCATGCTTCTTCTTCTTGCGTTACTCATTCTTGGGATAGTGTGGGTAGCTT
CAGCACTCATTGACAACGATGCCGCAAGCATGGAATCTTTATATGATCTCTGGGAGTTCTATC
TACCCTATTTATATTCCTGTATATCATTGATGGGATGTTTGTTACTTCTCTTGTGTACACCAG
TTGGCCTTTCTCGTATGTTCACAGTGATGGGTCAGTTGCTAGTGAAGCC

FIGURE 305

ATAGTATTAAGTCNATTGNGCAAGTGNAGCCTTAGAAGATTTGGAGTGTTTTTNACTCTTTTT
CNTGGTGGCTTAGAATTTTCTCCAAGAAAAGTTAAGAAAGGTGTGAAGATTTCCTTACAAGGN
CCGTGTACATGACACTGTTAATGATTGCATTTGGCTTGCTGTGGGGGCATCTCTTGCGGATCA
AACCCACGCAGAGCGTCTTCATTTCCACGTGTCTGTCCTTGTCAAGCACACCCCTCGTGTCCA
GGTTCCTCATGGGCAGTGCTCGGGGTGACAAAGAAGGCGACATTGACTACAGCACCGTGCTCC
TCGGCATGCTGGTACGCAGGACGTGCAGCTCGGGCTCTTCATGGCCGTCATGCCGACTCTCAT
ACAGGCGGGCGCCAGTGCATCTTCTAGCATTGTCGTGGAAGTTCTCCGAATCCTGGTTTTGAT
TGGTCAGATTCTTTTTTCACTAGCGGCGGTTTTTCTTTTATGTCTTGTTATAAAGAAGTATCT
CATTGGACCCTATTATCGGAAGCTGCACATGGAAAGCAAGGGGAACAAAGAAATCCTGATCTT
GGGAATATCTGCCTTTATCTTCTTAATGTTAAC

FIGURE 306

AACCTATATAAAATAGTTTTTAGCAGTTTATAGCTGTGACCATCAAGTCAGATAATTTGGGAT
GTTCACAGAGAGCTCTGGGTGATTATGACAGTGACCACCCACATCTCTTATTTGTTNTGCTTC
ATTTCTCTACTAGGGAGAGGAGGTCATATAATATATGGTATTTTTATGTTATTTTAGATAAAT
CCATATCAACACAGCACAGGAGAACNAATTATACCCCCTGGTAGATTTTGGGGTATAAACGTC
ATGAAATGTTTCTCAGAAAGTGAGAAATATTTCTTGATTGTATCTTTAAAATTAATGCAAAAT
TGTTATGTTACTCCATAATTTATTTGTGTGCATTACTGTAAGGTTCATGTGTATTCATATTAA
ATTTTTTCTTTTAAAAATTGGGTTCAATGAATTATCTAGGATGATTGCATTGTTTGTGGCATC
AAGTGTTGTTTCTCCCTTTCCATACCAAGCATATCCTGCTTTTGGTACAGG

FIGURE 307

TTACTTGTGAGTATCATCNTGTCCTTTAATCCTGTACCCTAAAATAAGNAATACATTTTTGAC
ANAGGCTTAATGTTTTAACAAAAGAGTGTGGACATTTTTATTTTAAAATTTAGGCAAAAGTCA
CTATCAAATGGTTGCTTATTTGTCTCACACANCCATATAGTTTTTCCTGGANGGTTTTGTTTT
GTTGTTGTTGAAAAGACTTTGNTTACAGNTANATGNAACCTTTTTATAGAAAAAAAAAAATTGT
TGAAAGGTCCAGTTCTCAGTACCATGTGAGTTAATGATACTACAACTAAGTTCTTTTTAAAAA
GTGATTAATGTATTTTATAAATTACCTTTTCACATATGCAAAATCTGTTTCTACTACAATGTT
ATTTTTACTAATGCCTTATTGTTGCACTCTTTTTGAAATATCCTGCAGTGAATATATGAATCA
ATTTGGGCTTAAAACTGAAAGCCAGTTGGCTGAAAGGTTTGAAATACGTACCCC

FIGURE 308

TTCTTTCTTTTCCCCATNTCATTCATTCAGGCTCCTTTCGCANAAGTGAGGTATTTAGATAAT
CAAAACCCCACACAAGACCTCAACAGCAAATACAGATGAAATGTAATTATTATTTCAATTAAA
AAGGGAATAATATTTGTAGGCCATTGTNACCAGTATTCTCTCGTTTTAACTAGTTTTGCTGCA
TTTAAATTAAGTGCTGCTCTTCAGCTTTTGTGTACAGCTATAAGTGCACATTGGAATTTATAT
GTATATATATATAGAGAGAGAGAGAGAGAGAGAGAAAATGACTGCTGGTTCAGTGTGTGTCCCTC
AGATCATACCACTACGAGTGCCTCAGCCTGGAAAAGCTAACCATGAAATTGATAACAATACGC
TTTTGGAAATGAAATCAGGTAAGAATCACATATGTTTGAAATTGTTTAAAATAACATTGTCAT
ATTTCTTGTGTTATCTGGTTGCTGGTTTATCTCTTTG

FIGURE 309

GTGGCCCGTCTGGCTAGTCCTGTNTAAGCGCGCCCATTTCGAGCCCAAGTTTCCAGCTCGGGT
TTCCGGGCTCAGAATTTTCCAGGAGTGGGTTCTTGGGCAGTGGCTGTGGAACAGGAATGGCGC
AGCTANAGGGTTACTGTTTCTCGCCGCCNTTGAGCTGTACCTTTTTAGTGTCCTGCCTCCTCT
TCTCCGCCTTCAGCCGGGCGCTGCGAGAGCCCTACATGGACGAGATCTTCCACCTGCCTCAGG
CGCAGCGCTACTGTGAGGGCCATTTCTCCCTTTCCCAGTGGGATCCCATGATTACTACATTAC
CTGGCTTGTACCTGGTGTCAGTTGGAGTGGTCAAACCTGCCATTTGGATCTTTGGATGGTCTG
AACATGTTGTCTGCTCCATTGGGATGCTCAGATTTGTTAATCTTCTCTTCAGTGTTGGCAACT
TCTATTTACTATATTTGCTTTTCCACAA

FIGURE 310

CGCNTCGGCCCATGNACGCCTTGTGCGGTTCCGGGGAGTCGGCTCCAAGTCTGGGACTCCAAC
CTGTCTGTGCACACAGAAAACCCGGACCTCACTCCCTGCTTCCAGAACTCCCTGCTGGCCTGG
GTGCCCTGCATCTACCTGTGGGTCGCCCTGCCCTGCTACTTGCTCTACCTGCGGCACCATTGT
CGTGGTACATCATCCTNTCCCACCTGTCCAAGCTCAANAATGGTCCTGGGTGTCCTGCTGTGG
TGCGTCTCCTGGGCGGACCTTTTTTACTCCTTCCATGGCCTGGTCCATGGCCGGGCCCCTGCC
CCTGTTTTCTTTGTCACCCCCTTGGTGGTGGGGGTCACCATGCTGCTGGCCACCCTGCTGATA
CAGTATGAGCGGCTGCAGGGCGTACAGTCTTCGGGGGTCCTCATTATCTTCTGGTTCCTGTGT
GTGGTCTGCGCCATCGTCCCATTCCGCTCCAAGATCCTTTTAGCCAAGGCAGAGGGTGAGATC
TCAGACCCCTTCCGCCTCAC

FIGURE 311

CCATCAGGAAGGTGAAAGAGGTCTTTGGGACAGGGGCCATGAGACATGTGGTCATCCTCTTCA
CCCACAAAGAGGACTTAGGGGGCCAGGCCCTGGATGACTATGTAGCAAACACGGACAACTGCA
GCCTGAAAGACCTGGTGCGGGAGTGTGAGAGAAGGTACTGTGCCTTCAACAACTGGGGCTCTG
TGGAGGAGCAGAGGCAGCAGCAGGCAGAGCTCCTGGCTGTGATTGAGAGGCTGGGGAGGGAGC
GAGAGGGCTCCTTCCACAGCAATGACCTCTTCTTGGATGCCCAGCTGCTCCAAAGAACTGGAG
CTGGGGCCTGCCAGGAAGACTACAGGCAGTACCAGGCCAAAGTGGAATGGCAGGTGGAGAAGC
ACAAGCAAGAGCTGAGGGAGAACGAGAGTAACTGGGCATACAAGGCGCTCCTCAGAGTCAAAC
ACTTGATGCTTTTGCATTATGAGATTTTTGTTTTTCTATTGTTGTGCAGCATACTTTTTT

FIGURE 312

TCTTTGTTCTCACAAGTTATCTTTACATTGGAATGACCCTGAATTAGGAAGTTAAAGTGAACT
TGGTTGGATTTGGATACTGCTNTAAAAGTTAGAAAATTAGGTCATTTGACATTTNTGCTCCGT
GTTTTGCCATGTTTGGTTCCTACATACTTTTGCAAAGATCAAGGAAGACCTTTGAGGCATCTC
TTTATCTCTTATTTCTATTACTATCACCCCAATTCAAGTCATCATCATTACCCTGGACTTCTG
GGATAGCTTCCCACTGTTCCCACTCATCTACTCTTGCTCACTGCCTTCCCCCCAAACCCCCTA
AAATTCATTCTCCAGATAGTGACTAGAGTGAATCGACTATATCTTCTCTTTTCCTGCTCTGGA
TATAATTTATATCTTTTCCTGCTCTGGATATAATTTATATCCTTCATTCTCCATTTCTGTGCC
CCTGTGTGCCAACTGCTATTGTCTGCATTAGATGGACTTCCTTATCTTCTGGCTTCTATTGAA
TTTGGTGAACTGGGGAGGGTCAAGTAGGAGATCAGTGTGTGGGAGAAGAAAGAAGTTTGAGTA
TTTATCACCTAGGAAGGGGGACTTCCAGGACACTGTTTGGCAGGGATGCTGGGCCTCTACTGG
AGGCCTAGTTCCGACTGTGTTGCCC

FIGURE 313

TTTTTTTTTTTTTTTTTTTTGGATTAATGAGGAAATCATTCTGTGGCTCTAGTCATAATTTATG
CTTAATAACATTGATAGTAGCCCTTTGCGCTATAACTCTACCTAAAGACTCACATCATTTGGC
AGAGAGAGAGTCGTTGAAGTCCCAGGAATTCAGGACTGGGCAGGTTAAGACCTCAGACAAGGT
AGTAGAGGTAGACTTGTGGACAAGGCTCGGGTCCCANCCGGACGNGTGGG

FIGURE 314

ATTTGGGTTTTTTTTTTCCAAAAATTGCTGAAATATTGTTTTGCCATTTTTAAAAAGTCTCAG
GTTATTACCACTCTGCCATTAAATATTTGTATGCCTGCATTTTTAAAAATTCTGTGCATGTAC
TTTATGGAGTACATTCTATTTTTGTTTTCAGATACCCCGGACGCGTGGG

FIGURE 315

CGGACGCGTGGGGAAACCTTGCCTTCAAGGGTTTTTTGTTTTGTTTTGTTTTGTTTTTTGTTT
GTTTGGGTTTGTTTTGTTTTGGTTTGGTTTTGAAACGGAGTCTCGCTCTGTCGCCCAGGCTGG
AGTGCAGTGGCGCAATCTCGGCTCACTGCAAGCTCCGCCTCCCGGGTTCACGTCATTCTCCTG
CCTCAGCCTCCCGAGTAGCTGGGACTACAGGCGTCCACTACCACGCCTGGATAATTTTTTGTA
TTTTCAGTANAGACGGGGTTTCACCGTGTTAGCCAGGATGGTCTTGATCTCCTGACCTCATGA
TCCCGCCTGCCTCGGCCTCCCAAAGTGTTGGGATTACAGNGCGTGAGCCACCGNGCCGGGCAC
CTTCAAGGTTTTGTTAATTTTGGATAATGCTACAATCCGTTGCTGCAAAGAACTCGAAAATGC
ACACGCCAACATAGGAGTTCTTTTTATGCCCCCAAACATTAAGTNTTTCATCCAACCCCTCAA
TCGGGGCATAATAAAAGCATTCAAGGCACACTACNACAAGGGAGCTTTATATGAAGGCCTGTG
AGGCTCTCAGGACCAACAAGGAAACCACCATGCTGGACTATTGGAAGTCGGTCACTACATGCA
ACGTTATTGATTATGTCAGTACAGCCTGGGAGAGCATTGGTCAGGCTACTACCAATAACTGTT
GGGAAAATGTTTGGCCAGACTGCGTGGAGAATTTTGAAGGGTTTGAAGGTGTTACAGAAAATA
TAAAGAACACTGTCAGAGACATAATGCATATGGCACAGCAGGTAAGTGGAGAGGGCTTTGATG
ACGTGAAGGAAGGAGATGTGGAGTACATTTTGGCAGAGAAGGCAGTGGAACCAACCAACGAAG
ACCTGGATGAGATGGCAAAACAAGGCATTGGAGTTGATGGCCATGAAAGTCGGCCCAAGACTT
CCAGAATTGTCCCTCTCACAGCGCCC

FIGURE 316

AAATTCTACTTCCTGGATTTTGGAAGGCCAAAACATTTTTTCCCCATGGGATACATCCCCATG
TTTNTGGCACAATCCTTCTTTGAAAATAATATGGAACTTAGATATATTTAGNCATTACGTTCN
TCTGGNTGNATGACATCATTCAAGAGCTTTTCAAAGCATTTGTTCAGATCTTCAGTACTGGCC
AGTTTTCATACAGTCTCGGGGTTTTAAAACTTTGAAATCAAGGACACGACGTCTCCAGTCTAC
CTCCGAGAGATTAGTTGAAACNCAGAATATAGCGCCATCATTCGTGAAGGGGTTTCTTTTGCG
GGACAGAGGATCAGATGTTGAGAGTTTGGACAAACTCATGAAAACCAAAAATATACCTGAAGC
TCACCAAGATGCATTTAAAACTGGTTTTGCGGAAGGTTTTTCTGAAAGCTCAAGCACTCACAC
AAAAAACCAATGATTCCCTAAGGCGAACCCGTCTGATTCTCTTCGTTCTGCTGCTATTCGGCA
TTTATGGACTTCTAAAAAACCCATTTTTATCTGTCCGCTTCCGGACAACAACAGGGCTTGATT
CTGCAGTAGATCCTGTCCAGATGAAAAATGTCACCTTTGAACATGTTAAAGGGGTGGAGGAAG
CTAAACAAGAATTACAGGAAGTTGTTGAATTCTTGAAAAATCC

FIGURE 317

CGCTTGGGCAGGTTGGGGTTGAAACTNTTCACCCCTTGCGGTNTGTACTGCNTCCCAANTGAG
CAGCCAGGAGAAGGCTAGAGCCTGTGCCTTTCAGCTAGATAGCTGGAGGAACTGGTCCTCCCT
CCTTAGGCTGTGCTGGCCTGAGCTGGGAGCCTGAGAGCTGGGGCAGTTGTCTCTAAAGTGGCT
TCTGGGATTCTGGTAAGAGCGTTACATCCTTACTATTCAAAGTGCCATCCACAGACCTGCTGA
TGGGCAGCATGAGCATCACCTGGGAGCTTGCTGCGCTGTAGAATCTTGAGGGGTCTCCATCCA
GATCAGCTGAATCAGAGTTTGCATTGTTAACAAGATTCTGCTTCTCAGAAGATGCACTATTAT
AGATACTCTAACGCCAAGGTCAGCTGCTGGTACAAGTACCTCCTTTTCAGCTACAACATCATC
TTCTGGTTGGCTGGAGTTGTCTTCCTTGGAGTCGGGCTGTGGGCATGGAGCGAAAAGGGTGTG
CTGTCCGACCTCACCAAAGTGACCCGGATGCATGGAATCGACCCTGTGGTGCC

FIGURE 318

NTGCAGTCAACGCAGCTTCCCGGGTTCAGCCTGGGAANATGCGCGAATCGGNAACCCCAGAGC
CCGGTGGTTAGACCGGGGTCCGCCGCTTCCCCCACAGCCCNTTTCCTAATCGTTCAGACGGAG
CCTGGTCGACTTCGCCGGAGACTGCCAGATCTCGTTCCTCTTCCCTGTGTCATCTTCTTAATT
ATAAATAATGGGGGATGAAGATAAAAGAATTACATATGAAGATTCAGAACCATCCACAGGAAT
GAATTACACGCCCTCCATGCATCAAGAAGCACAGGAGGAGACAGTTATGAAGCTCAAAGGTAT
AGATGCAAATGAACCAACAGAAGGAAGTATTCTTTTGAAAAGCAGTGAAAAAAAGCTACAAGA
AACACCAACTGAAGCAAATCACGTACAAAGACTGAGACAAATGCTGGCTTGCCCTCCACATGG
TTTACTGGACAGGGTCATAACAAATGTTACCATCATTGTTCTTCTGTGGGCTGTAGTTTGGTC
AATTACTGGCAGTGAATGTCTTCCTGGAGGAAACCTATTTGGAATTATAATCCTATTCTATTG
TGC

FIGURE 319

TCAGCGGGTAAGAAAATTCTACTTCCNGGGATTTTTGTAAAAGGCAAAAACCTTTTNTTCCCC
ATTGGCATACATTCCCAANGTTTNTGCCCAATCCTTCTTTTGAAAATTAAATATGGAACTTAG
ATATATTTAGTCATTACGTTCNTCTGGCTTGTATGGACATCATTCAAGAGCTTTTCAAAGCAT
TTGTTCAGATCTTCAGTACTTGGCCAGTTTTCATACAGTCTCGGGGTTTTAAAACTTTGAAAT
CAAGGACACGACGTCTCCAGTCTACCTCCGAGAGATTAGCTGAAACACAGAATATAGCGCCAT
CATTCGTGAAGGGGTTTCTTTTGCGGGACAGAGGATCAGATGTTGAGAGTTTGGACAAACTCA
TGAAAACCAAAAATATACCTGAAGCTCACCAAGATGCATTTAAAACTGGTTTTGCGGAAGGTT
TTTCTGAAAGCTCAAGCACTCACACAAAAAACCAATGATTCCCTAAGGCGAACCCGTCTGATT
CTCTTCGTTCTGCTGCTATTCGGCATTTATGGACTTCTAAAAAACCCATTTTTATCTGTCCGC
TTCCGGACAACAACAGGGCTTGATTCTGCAGTAGATCCTGTCCAGATGAAAAATGTCACCTTT
GAACATGTTAAAGGGGTGGAGGAAGCTAAACAAGAATTACAGGAAGTTGTTGAATTCTTGAAA
AATCC

FIGURE 320

GCCNAGCGGACGGGCCGCTTAAACGGGCTGCTCGTGCCGATTCTTTTACCTGAGAAATGCTAC
GACCAACTTTTCGTTCAGTGGGACTTGCTTCACGTCCCCTGCCTCAAGATTCTCCTCAGCAAA
GGCCTGGGGCTGGGCATTGTGGCTGGCTCACTTCTAGTAAAGCTGCCCCAGGTGTTTAAAATC
CTGGGAGCCAAGAGTGCTGAAGGGTTGAGTCTCCAGTCTGTAATGCTGGAGCTAGTGGCATTG
ACTGGGACCATGGTCTACAGCATCACTAACAACTTCCCATTCAGCTCTTGGGGTGAAGCCTTA
TTCCTGATGCTCCAGACGATCACCATCTGCTTCCTGGTCATGCACTACAGAGGACAGACTGTG
AAAGGTGTCGCTTTCCTCGCTTGCTACGGCCTGGTCCTGCTGGTGCTTCTCTCACCTCTGACGCC

FIGURE 321

GTTGGCCTGATTCTCCCCACCAGAGGACAGACGTTGAAAGATACCACGTCCAGTTTTCAGCAG
ACGCAACTATCATGGACATTCAGGTCCCGACACGAGCCCCAGATGCAGTCTACACAGAACTCC
AGCCCACCTCTCCAACCCCAACCTGGCCTGCTGATGAAACACCACAACCCCAGACCCAGACCC
AGCAACTGGAAGGAACGGATGGGCCTCTAGTGACAGATCCAGAGACACACAAGAGCACCAAAG
CAGCTCATCCCACTGATGACACCACGACGCTCTCTGAGAGACCATCCCCAAGCACAGACGTCC
AGACAGACCCCCAGACCCTCAAGCCATCTGGTTTTCATGAGGATGACCCCTTCTTCTATGATG
AACACACCCTCCGGAAACGGGGGCTGTTGGTCGCAGCTGTGCTGTTCATCACAGGCATCATCA
TCCTCACCAGTGCGGACGCGTGGGCGGACGCGTGGG

FIGURE 322

CAGTGCCTTTAGATTGTGTTTTGCCTCCTCCAATGTAGAGTTGACATNTGGACCCCAGAGCCC
AGCAGGGCTTTNTGTCAGACATGTAGGGTGGTAGAAATGGGCCCTCCAGGTCCCCCTGCAGTG
CACTGGGCAGAGACCTCCGGAAAGCCGGCAGCGGGAGCGCTTCCTGGGCAGCTTCCCCCAGCA
CAGTGTTCCCAAACCAGTCCATCCGGAAAACAGTCTGTACAGCAAATGCTGTGTGAGATCTTA
GGCTTTTCACTTTTTTTTGTTTTGTTTTGTTTTTGAAAGAAAGAAAAAAATACAATTAACAAG
CCTCTTTTGTAAATGGGTTTCCTTTCTATGTATAAAATCGTGGTGGTCCCTTGTTTTTACATG
TTCATGCTGTGTAATTTTGAGATGTTACTGAGATATGTTCTGAACATAATGTGCATTTTTTTC
TGTACAGATGAAATGGGAGAATTTAATAAAGAGTTTGCAGCCCACGCGTCCGCGGACGCGTGGG

FIGURE 323

GAAGTGTTCACTGGACAATTNGCAAGTTAGGTCCAGTTCCAGTTGGAGGATTCTTCCATTGTT
CCAAGGTGTGGNAATTNCAATGGTCCTGATCTCCATTTTTGTGNCAATCTATTNCAATGTCAT
AATTGCCTATAGTCTTTACTACATGTTTGCTTCTTTTCAAAGTGAACTACCATGGAAAAATTG
TTCTTCGTGGTCAGATAAAAACTGTAGCAGATCACCAATAGTAACTCACTGTAATGTGAGTAC
AGTGAATAAAGGAATACAAGAGATCATCCAAATGAATAAAAGCTGGGTAGACATCAACAATTT
TACCTGCATCAACGGCAGTGAAATTTATCAGCCAGGGCAGCTTCCCAGTGAACAATATTGGAA
TAAAGTGGCGCTCCAACGGTCAAGTGGAATGAATGAGACTGGAGTAATTGTTTGGTATTTAGC
ACTTTGTCTTCTTCTGGCTTGGCTCATAGTTGGAGCAGCACTATTTAAAGGAATCAAATCGTC
TGGCAAGGTGGTATATTTTACAGCTCTTTTCCCCTATGTGGTCCTACTCATCCTGTTAGTACG
AGGTGCAACTCTGGAGGGTGCTTCAAAAGGCATTTCATACTATATTGGAGCCCCGGACGCGTGGG

FIGURE 324

CGGGGGGCNTACACCACTGCCTGNGTCTTCACCACCGCCGCCGTGCAGTTGGAATTGATCACA
CCTTTTCAGTTGTACTTCAATCCTGAATTAATCTTTAAACACTTTCAAATATGGAGATTAATC
ACCAACTTCTTATTTTTTGGGCCAGTTGGATTCAATTTTTTATTTAACATGATTTTTCTATAT
CGTTACTGTCGAATGCTAGAAGAAGGCTCTTTCCGAGGTCGGACAGCAGACTTTGTATTTATG
TTCCTTTTTGGTGGATTCTTAATGACCCTTTTTGGTCTGTTTGTGAGCTTAGTTTTCTTGGGC
CAGGCCTTTACAATAATGCTCGTCTATGTGTGGAGCCGAAGGAACCCCTATGTCCGCATGAAC
TTCTTCGGCCTTCTCAACTTCCAGGCCCCCTTTCTGCCCTGGGTGCTCATGGGATTTTCCTTG
TTGTTGGGGAACTCAATCATTGTGGACCTTTTGGGTATTGCAGTTGGACCGGACGCGTGGG

FIGURE 325

TGCAAATTNTGAGATTCAGAGACTAAAGTAATTTATTTATACATAGCTAATCAGTGCCAGAGC
TGTGAATCTAAGATTATCTTGCTCTTAATCACAAAAATACACAGTTATTAGTTGTTTGCATTT
GATGCAAATGACTTGGAACCCACACATTTTACACATTTTTAATGAATGAAATGACTAGTTTGA
TTCATTACACGTTTGTGGAAATTTTGCAGCTAGGTTTTAAATTAAGAACACCAGATTTATTTA
AATACAATTTAAAATCATTGTATTCCAAATGGAAGTTTTCTTCTATAAGAATACCAGGCTGGA
TGTGGTGGCTCACACTTGTAATCCTAGCACTTTGTGTGGCCGAGGAAGCGGACGCGTGGG

FIGURE 326

GTCAGGATTTTTGAAGTTTTTTTTTTATAGTGAGATAATGGAGTTGGTCTTAGCCGCTGCAG
GAGCCCTTCTTTTCTGTGGATTCATCATCTATGACACACACTCACTGATGCATAAACTGTCAC
CTGAAGAGTACGTATTAGCTGCCATCAGCCTCTACTTGGATATCATCAATCTATTCCTGCCGG
ACGCGTGGG

FIGURE 327

CAAGTTAGGTGATCCAGNTTTTGTGGTCTTTTGCAACCCTTGTGGTCATTGTGCCCTTGATAT
TAATCTTCGTGGTGGGTCCTCGCCATGGCAGACAAACATTCTTGTGTACATAACAATCTGCTC
TGTAATCGGCGCGTTTTCAGTCTCCTGTGTGAAGGGCCTGGGCATTGCTATCAAGGAGCTGTT
TGCAGGGAAGCCTGTGCTGCGGCATCCCCTGGCTTGGATTCTGCTGCTGAGCCTCATCGTCTG
TGTGAGCACACAGATTAATTACCTAAATAGGGCCCTGGATATATTCAACACTTCCATTGTGAC
TCCAATATATTATGTATTCTTTACAACATCAGTTTTAACTTGTTCAGCTATTCTTTTTAAGGA
GTGGCAAGAGATGCCTGTTGACGATGTCATTGGTACTTTGAGTGGCTTCTTTACAATCATTGT
GGGGATATTCTTGTTGCATGCCTTTAAAGACGTCAGCTTTAGTCTAGC

FIGURE 328

AAAGTGGTCCTTTTAGGGTAAAGAGTTTTAAAGAGTTTAATGNGTNTATGGCAGGTTTGGGAA
AGGTAAGAAATGGGTCCTTTTTCCTCCTAATGTTTTTGGCACTTAAAACATAAAATTCATTAT
CCTATTAAAAAATTAAATTCAGTTTGCTAATCCAGAAATTGTTCCCAAATGAAAACTTGTTTT
AAGTCCACCCCTTAGTTTCCTTATTTTACAAGGTCTCTCTTCAGGGACCAACAGGGGCTTAGA
GAGCCTTAGTTAGATTAAAGGGAGACCCTACCTCTTAAAACCAGTTTTCATTTATGCAAACAA
GGACAATTAAGGGAACCCTGACCCCACAGGCTCTCAAGTCTTCCCAAGGCCAGAATCGAAAGA
AAATTAAAATTTGAATGCTGAATATTCTGGCTCTACTCTGGCCTTTTTTTCTGGTTCCCTTCC
AAAATGCACAAATCATACCCTTGTCTGCTCCAATTCAGTCTCCAAACCTGGTGCCTGTGCTCC
TGGCCCCCCTAGCATCATGCTATCCCAGGAGTATCAGGACCAGACACATCCACGG

FIGURE 329

GGCNACGGCGGCCNAAGACGGACATGAAGCAATATCAAGGTTCCGGCGGGGTCCCCATGNATG
TGGAACGNAGTCGCTTTCCCCTACTGCGTGGTGTGNACGCCCATCCCGGTGCTCACGTGGTTT
TTCCCCATCATCGGCCACATGGGCATCTGCACATCCACAGGAGTCATTCGGGACTTCGCGGGC
CCCTACTTTGTCTCAGAGGACAACATGGCCTTTGGAAAGCCTGCCAAGTACTGAAGTTGGACC
CTGCTCAGGTCTATGCTAGCGGGCCCAACGCATGGGACACGGCTGTGCACGACGCCTCTGAGG
AGTACAAGCACCGCATGCACAATCTCTGCTGTGACAACTGCCACTCGCACGTGGCATTGGCCC
TGAATCTGATGCGCTACAACAACAGCACCAACTGGAATATGGTGACGCTCTGCTTCTTCTGCC
TGCTCTACGGGAAGTACGTCAGCGTTGGGGCCTTCGTGAAGACCTGGCTGCCCTTCATCCTTC
TCCTGGGCATCATCCTCAC

FIGURE 330

TTTGATTTAATGTTGGTTGTGTGTCTCCTCCTGGCAACTGGATTTTGCCTGTTCAGAGGTTTG
ATTGCTTTGGATTGCCCATNTGAGCTCTGCCGATTATATACGCAATTTCAAGAGCCCTATNTA
AAGGATCCTGCTGCTTATCCTAAAATTCAGATGCTGGCATATATGTTCTATTCTGTTCCTTAC
TTTGTGACTGCACTGTATGGCTTAGTGGTTCCTGGATGTTCCTGGATGCCTGACATCACATTG
ATACATGCTGGAGGTCTGGCTCAGGCTCAGTTTTCTCACATTGGTGCATCTCTTCATGCTAGA
ACTGCTTATGTCTACAGAGTCCCTGAAGAAGCAAAAATCCTTTTTTTAGC

FIGURE 331

GAAAATATCTGGAGGTACTGCACATAAGGATTCCAATTTCTATTTTCAGAACTTTCATTTGTA
ATTTATGTACGCATCTAACGTCTATTTACGTGTATACTGAGTTAGGGTGTACAACTTTTCCCT
GAGGCTGTATCTCAAAAACTTTGGAAGCTGAAGAATTTGTCCAAATCTATGTTCCTTTTTGTT
TGTAAATCACCTGATGATGGTGATATAGCTGTGGCCAACGAAATGTCAAGGGAAGTCTGCTGG
GGAAGGTAGACGTAGGATAGGAGTATGGGAAAAAATTATTCACTCAAAAGCATGATGCACAGA
GGAGCTATGATCTTTTCTTGTTTTCCTCACTGGATGTTGTCATGTCTGTATGTACTTCCTGGA
ACTGTGGCACCATCTTACAACCATGAAAGGAGCTCACATGAAATCATGTTGAACATAGCAGAG

FIGURE 332

AGGTTGGTCCTTTTCCGGTTTTTTGGCCAATTTCAAGTTTCCAGNNTCCATNATCCAAGTTTG
AAGCCCCNTGGCGGATCCTTAAAAATCCCTGACCTGACCAGGGTCGCCAAGGGTCGCACAAGG
CCTGGGCCAGGTTCCCACAGGGAGGTGAAAAAACTCCCATTCCGTTNAAAAGCAGTTTCCTTT
GGGACCCATTTCCTTTTCCCTTTGGCCATGGCCGTGNCCTCCAAAGGTTCCGGTAGTTTAATG
CAAATGTTCTACCAATAGCCCCNAGAACTCCACCACCCTCTCTCTGTCTTGTGGCTCAAGTCG
AGCAACCTGAAAGGATATATTTTTTCAAATAAGTAATTCCTGTAGGCAATAAAAAGATACACT
ATCTTCTGAGTGAAATATAAAGAGTTCACAGCAGCTGTCTCCCCAGTTTGCATTTTCCTCTGC
ACCTGATGGGAAGGACAGATAAAGATAATGGGATTTTTTCTTTATTTTTTATTTCACCTCCCT
CTCTCCCTGGAAGGTGGAAATGTAACAAATTGGATTGTGAGTGTGTCTGTCCTTTGTGCTTGG
TGCCTGGAGCAGGGCATCCGGCTGCCGGGCAGAGCTGCTGCGAGAGAGGTCAGAGCTACC

FIGURE 333

CCAAGTTGAAGCCCATGGCGGTCCTTAAATCCTGCCTGACCAGGGTCGCCAGGGTCGGGCAAG
CAAGTGCCAGAAGAATAAAGAAGATGGACGCAAAAAGAAGAAAGGAAGNNCCAGAAGAGACGA
AGAGATGAAACGACAGTCAGATGANATGAGGAGGAAAGAAAGGTTTCANAAAGCCGNCGGAAA
TGAAAGNCGTCCTGGTTTGAANGAANTTGCCAANAGATAAATCCAGCAGGANAGGCCNAGAAA
GATCGAGGTCTGCTTATCTGCTGTTACCTTGGACACCAGAGCAGCTATAGGTATCTGCCAGAG
CTATGAAATCATTCAGCCGGATCCTCTTCCTCGTCTTCCTCCTCGCCGGCCTGAGGTCCAAGC
CGCTCCCTCAGCCCCTCTGCCTTTGGGCTGTGGCTTTCCGGACATGGCCCACCCCTCTGAGAC
TTCCCCTCTGAAGGGTGCTTCTGAAAATTCCAAACGAGATCGCCTTAACCCAGAATTTCCTGG
GACTCCTTACCCTGAGCCTTCCAAGCTACCTCATACGGTTTCCCTGGAAACCTTCCCACTTGA
CTTCACTGAGCCCCTCAACCCTGACCTCCGAGAAACCCCG

FIGURE 334

TTCAGACTCACTGAATCAGAACCNTGGGATAGGCCAGCACGCTGTGCTTTACCAAGCTCTAGG
TGATGCCAATTCATACTCAAGTGTGAGGCTGACTGGCTTATTTGAAGGGAGAGAAAGGAACAG
GCACATGGCGACATATCAGCATTTACACAAGGCGTGCTGGGTAACCATAGGAACACCTTTATT
ACGGTTAAATAGGAAACAGGCATCAATGCAGAGGGCCCCCAGGAGAATCAGGAAGGTCGCGAC
TGTCACTGTCTGAGGGCACTGTTGTGAAACGATGGCCGAAGGTGACAACCACAGCAAAGTTTC
AAGGAAGTTCACTGAAACGTGGAAAAACCCACTCAATGTCCTGCTCTCATTTATATTGAGTGG
CTTAAGTATTTATTTTCTTGGTTTTTTAGAGGAAGGGAG

FIGURE 335

GAAGCTTCCGTTGCCAAGCGACATGTTCAAGGTAATTCANAGGTCCGTGGGGCCAGCCAGCTT
GAGCTTGCTCACNTTCAAAGTCTATGCAGCACCAAAAAAGGACTCACCTCCCAAAAATTCCGT
GAAGGTTGATGAGCTTTCACTCTACTCAGTTCCTGAGGGTCAATCGAAGTATGTGGAGGAGGC
AAGGAGCCAGCTTGAAGAAAGCATCTCACAGCTCCGACACTATTGCGAGCCATACACAACCTG
GTGTCAGGAAACGTACTCCCAAACTAAGCCCAAGATGCAAAGTTTGGTTCAATGGGGGTTAGA
CAGCTATGACTATCTCCAAAATGCACCTCCTGGATTTTTTCCGAGACTTGGTGTTATTGGTTT
TGCTGGCCTTATTGGACTCCTTTTGGCTAGAGGTTCAAAAATAAAGAAGCTAGTGTATCCGCC
TGGTTTCATGGGATTAGCTGCCTCCCTCTATTATCCACAACAAGCCATCGTGTTTGCCCAGGT
CAGTGGGGAGAGATTATATGACTGGGG

FIGURE 336

GGCGGCCGAGGCGGACGGCCGCTTAAACGGCTGCTCGTGCCGATTCTTTTACCTGAGAAATGC
TACGACCAACTTTTCGTTCAGTGGGACTTGCTTCACGTCCCCTGCCTCAAGATTCTCCTCAGC
AAAGGCCTGGGGCTGGGCATTGTGGCTGGCTCACTTCTAGTAAAGCTGCCCCAGGTGTTTAAA
ATCCTGGGAGCCAAGAGTGCTGAAGGGTTGAGTCTCCAGTCTGTAATGCTGGAGCTAGTGGCA
TTGACTGGGACCATGGTCTACAGCATCACTAACAACTTCCCATTCAGCTCTTGGGGTGAAGCC
TTATTCCTGATGCTCCAGACGATCACCATCTGCTTCCTGGTCATGCACTACAGAGGACAGACT
GTGAAAGGTGTCGCTTTCCTCGCTTGCTACGGCCTGGTCCTGCTGGTGCTTCTCTCACCTCTG
ACGCC

FIGURE 337

CGGAACGCGTGGGCGNACGCGTGGGCAAGATGTCCCTGTGGACTCCCAAACTCTACTCCAGAT
GGGNAGGTGCCCTTAACACCAAGATTTTAAAAGCTCCAATTTCAGAGCAAGAGTCGAAAACTC
ACAGATAAAGTTATAGTTATTTCAGGGTTCTGAAAAGACGCAGAACATGAAGGGACTCAGAAG
TCTGGCAGCAACAACCTTGGCTCTTTTCCTGGTGTTTGTTTTCCTGGGAAACTCCAGCTGCGC
TCCGCAGAGACTGTTGGAGAGAAGGAACTGGACTCCTCAAGCTATGCTCTACCTGAAAGGGGC
ACAGGGTCGCCGCTTCATCTCCGACCAGAGCCGGAGAAAGGACCTCTCCGACCGGCCACTGCC
GGAAAGACGAAGCCCAAATCCCCAACTACTAACTATTCCGGAGGCAGCAACCATCTTACTGGC
GTCCCTTCAGAAATCACCAGAAGATGAAGAAAAAAACTTTGATCAAAC

FIGURE 338

CCNTGCACAAGCAGCACTTTCTTTTGCCATAGCAACATGTGCATCAATAATTCTTTAGTCTGT
AATGGTGTCCAAAATTGTGCATACCCTTGGGATGAAAATCATTGTAAAGAAAAGAAAAAAAGCA
GGAGTATTTGAACAAATCACTAAGACTCATGGAACAATTATTGGCATTACTTCAGGGATTGTC
TTGGTCCTTCTCATTATTTCTATTTTAGTACAAGTGAAACAGCCTCGAAAAAAGGTCATGGCT
TGCAAAACCGCTTTTAATAAAACCGGGTTCCAAGAAGTGTTTGATCCTCCTCATTATGAACTG
TTTTCACTAAGGGACAAAGAGATTTCTGCAGACCTGGCAGACTTGTCGGAAGAATTGGACAAC
TACCAGAAGATGCGGCGCTCCTCCACCGCCTCCCGCTGCATCCACGACCACCACTGTGGGTCG
CAGGCCTCCAG

FIGURE 339

AAATAAAGAACCATGGTATCATGTTGNTCAGTGCTTCAGACAGAAAGATTGTTGAAGCATCAA
GGAGAGCTTTTGTTATGTGGCAATGAACTACGAAGAGGAAATGGCCAAGAAACCCGATTGTCT
AGAGAAAGTTTACCAACTACCTGATGGGAAGGTCATCCAGCTCCATGACCAGCTCTTTTCTTG
TCCAGAGGCCCTCTTCTCTCCGTGTCATATGAACCTTGAGGCCCCTGGCATTGATAAGATATG
CTTCAGCAGCATAATGAAATGTGATACAGGCCTGAGGAATTCCTTCTTTTCCAATATTATCCT
TGCCGGGGGATCAACCTCTTTCCCTGGTTTAGACAAGCT

FIGURE 340

TGGCGGTCCTAAAATCCTGNCCTGACCAGGGTCCGGCGGTTCAGTTGGAGGAAAAGTGTAGCC
TTGCAGGTGGCAANTGGTCCAGGTACCGGTATTTGGCNGGCCCGTTTTTGCCTCCTCCTCCGT
GGGTGCGGCGGGAATNTTGGCCGGNCGGCCTTGGGACGGCCCAGGTCCCGGCCGCAAGGTCCG
GGCCAATACATAGTCATCAGTAGAAACTTCTTGAAGTTGTTCAAGAAAAATTTGAAAGTAGCA
AAATAGAAAATAAAGAATTAACAGCAGATACAGAGGCAGCATGAAGTGTTGTCTTAGGAAACA
GAACACAGCAGTGAAAAAACAGACAAAATCCGCTCAGATACAACTGCAGCTGATAATGTTTTC
CGGCTTCAATGTCTTTAGAGTTGGGATCTCTTTTGTCATAATGTGCATTTTTTACATGCCAAC
AGTAAACTCTTTACCAGAACTGAGTCCTCAGAAATATTTTAGTACATTGCAACCAGGAAAAGC
CTCTTTAGCTTATTTTTGTCAAGCTGATTCCCCAAGAAATACA

FIGURE 341

CCGAATCAAGTTCGAGTCATCCGTGTGGGCATTNGTCCCCCNTGGCACAGTTGGCTTCTTTCC
AGAAGCCCGTTTTGTTTGTTTTACGTCTAAATTCGCGTCGGTTCTTATTTCTCTCCCTGGCAA
GGTCTGAAGACGGGTAGGAGAATAACCTGTGTCAGCGTGTTATGATGCCGTCCCGTACCAACC
TGGCTACTGGAATCCCCAGTAGTAAAGTGAAATATTCAAGGCTCTCCAGCACAGACGATGGCT
ACATTGACCTTCAGTTTAAGAAAACCCCTCCTAAGATCCCTTATAAGGCCATCGCACTTGCCA
CTGTGCTGTTTTTGATTGGCGCCTTTCTCATTATTATAGGCTCCCTCCTGCTGTCAGGC

FIGURE 342

AGTTCCGGCAAGGGTGCATCCGGCNTGTGTGTGGCGCAAGGCAAGGAAACCGGTACCCGGGTC
CTGGCCCCAGCGCTGACGTTTTCTCTCCCCTTTCTTCTCTCTTCGCGGGTTGCGGCGTCGCAG
ACGCTAGTGTGAGCCCCCATGGCAGATACGACCCCGAACGGCCCCCAAGGGGCGGGCGCTGTG
CAATTCATGATGACCAATAAACTGGACACGGCAATGTGGCTTTCTCGCTTGTTCACAGTTTAC
TGCTCTGCTCTGTTTGTTCTGCCTCTTCTTGGGTTGCATGAAGCAGCAAGCCTTTACCAACGT
GCTTTGCTGGCAAATGCTCTTACCAGTGCTCTGAGGCTGCATCAAAGATTACCACACTTCCAG
TTAAGCAGAGCATTCCTGTCCCAGGCTTTGTTAGAGGACAGCTGCCACTACCTGTTGTATTCA
CTCATCTTTGTAAATTCCTATCCAGTTACAATGAGTATCTTCCCAGTCTTGTTATTCTCTTTG
CTTCATGCTGC

FIGURE 343

CCTGACCCAGGGTCCGGNGGCAATTTTCCATTTATGCCCTGTGGTNCGGGACATACCTAGATN
TCAGNCCATTTCCTCCAGGTTTTGGCCTTGTTTTAAGGCCCTGGGCTGGGATTNCAAGTGGCT
TGATCAACCCCCNTTTGGNCCAGTACTACCCTTAGGGNCCGTGACCNTGACTNTNTGCAGCAT
TTTCATACCTATCGGGTTGGGCGTCTTCATTCGCTACAAATACAGCCGGGGGCTGANTACATT
GTGAAGGTTTCCCTGTGGTCTCTGCTAGTGACTCTGGTGGTCCTTTTCATAATGACCGGCACT
ATGTTAGGACCTGAACTGCTGGCAAGTATCCCTGCAGCTGTTTATGTGATAGCAATTTTTATG
CCTTTGGCAGGCTACGCTTCAGGTTATGGTTTAGCTACTCTCTTCCATCTTCCACCCAACTGC
AAGAGGACTGTATGTCTGGAAACAGGTAGTCAGAATGTGCAGCTCTGTACAGCCATTCTAAAA
CTGGC

FIGURE 344

CCTAAATAGGGCCCTGGATATATTCAACACTTCCATTGTGACTCCAATATATTATGTATTCTT
TACAACATCAGTTTTAACTTGTTCAGCTATTCTTTTTAAGGAGTGGCAAGATATGCCTGTTGA
CGATGTCATTGGTACTTTGAGTGGCTTCTTTACAATCATTGTGGGGATATTCTTGTTGCATGC
CTTTAAAGACGTCAGCTTTAGTCTAGCAAGTCTGCCTGTGTCTTTTCGAAAAGACGAGAAAGC
AATGAATGGCAATCTCTCTAATATGTATGAAGTTCTTAATAATAATGAAGAAAGCTTAACCTG
TGGAATCGAACAACACACTGG

FIGURE 345

TTAAGTGCAAACCATGCAGTGCCCGAGGATGATACCATTAGCAATGACTCCAATGATTTCACC
GAAGTAGAAAATGGTCAGATAAATAGCAAGTTTATTTCTGATCGTGAAAGTAGAAGAAGTCTC
ACAAACAGCCATTTGGAAAAAAAGAAGTGTGATGAGTATATTCCAGGTACAACCTCCTTAGGC
ATGTCTGTTTTTAACCTAAGCAACGCCATTATGGGCAGTGGGATTTTGGGACTCGCCTTTGCC
CTGGCAAACACTGGAATCCTACTTTTTCTGGTACTTTTGACTTCAGTGACATTGCTGTCTATA
TATTCAATAAACCTCCTATTGATCTGTTCAAAAGAAACAGGCTGCATGGTGTATGAAAAGCTGGG

FIGURE 346

GCAGCATTCAGAGTTACTGGCTGTCATTTTTCATGGTGATGATTTTATTTGTAGCTTTCATAA
CCTGTTGGGAAGAAGTTACTACTTTGGTACAGGCTATCAGGATAACTTCCTATATGAATGAAA
CTATCTTATATTTTCCTTTTTCATCCCACTCCAGTTATACTGTGAGATCTAAAAAAATATTCT
TATCCAAGCTCATTGTCTGTTTTCTCAGTACCTGGTTACCATTTGTACTACTTCAGGTAATCA
TTGTTTTACTTAAAGTTCAGATTCCAGCATATATTGAGATGAATATTCCCTGGTTATACTTTG
TCAATAGTTTTCTCATTGCTACAGTGTATTGGTTTAATTGTCACAAGCT

FIGURE 347

ACAATGTTGGGTAAAATAATTGGGGGGGACTTTTGGGCCNTTCAGGNTTAATAGTATTAAGTC
TATGGGCAANTGGAGCCTTAGGANAATTTGGGGGGTTTTTAATCTTTTTCCTGGTGGGCTTAG
ATTTTTCTCCAGAAAAGTTAAGAAAGGTGTGAAGATTTCCTTACAAGGCCCGTGTTACATGCC
ACTGTTAATGATTGCATTTGGCTTGCTGTGGGGGCATTTCTTGCGNATCAAACCCACGCAGAG
GGTNTTCATTTCCAAGGTGTCTGTCCTTTGTCAAGCACACCCCTCGTGTCCAGGTTCCTCATG
GGCAGTGCTCGGGGTGACAAAGAAGGCGACATTGACTACAGCACCGTGCTCCTCGGCATGCTG
GTGACGCAGGACGTGCAGCTCGGGCTCTTCATGGCCGTCATGCCGACTCTCATACAGGCGGGC
GCCAGTGCATCTTCTAGCATTGTCGTGGAAGTTCTCCGAATCCTGGTTTTGATTGGTCAGATT
CTTTTTTCACTAGCGGCGGTTTTTCTTTTATGTCTTGTTATAAAGAAGTATCTCATTGGACCC
TATTATCGGAAGCTGCACATGGAAAGCAAGGGGAACAAAGAAATCCTGATCTTGGGAATATCT
GCCTTTATCTTCTTAATGTTAACGGTCACGGAGCTGCTGGACGTCTCCATGGAGCTGGGCTGT
TTCCTGGCTGGAGCGCTCGTCTCCTCTCAGGGCCCCGTGGTCACCGAGGAGATCGCCAC

FIGURE 348

AAAAAAAAAAAAAAAAAAAAAAGAACCACTTCTGCCTTATCATTCTCTCTTTATTACCGAAATG
CGGAGACAGAAAGTCAACAGAGAAAGAATTGTTTTCCCCAAGGCCACACAGATTGCTCCAACA
CTTGACTTTTCCTGCTAGGAACTCAATCCAAGAGATGGGCTTTCTTTTGTTCTCTGACTATAA
AAGGGTGTCACCTTGTCACCATCTTCTATCACACAGGACCCCTATGGGCTTGGTTTGGTTTTG
TTCTTTCATCATTATTATTTGGAAAGTTATATTTCCTTTACTGTCCTTGAGGTGTGAGGCTTC
ACCTCATCTTGTCTCCATATCCCTGAG

FIGURE 349

TGGATCCCATGGCCAGGGNGGCGTCCAGGTGCAAACCAGTAGAACNCAAGGCCTGAACCTGGG
GCCAGACACCTTGTTTTCCCCGGCCATGGTCAAGACCNTCCAGTACNTGCCTTACTGTGGGCC
CAGAANTGGGCCAAGTCTTGGCAGCCCGTGCCGCAGGTTGTTGTGCAGTTTGGGGTGTTCTTC
TGCACCATCCTCCTTTTGCTCTGGGTGTCTGTCTTCCTCTATGGCTCCTTCTACTATTCCTAT
ATGCCGACAGTCAGCCACNTCAGCCCTGGCATTTCTACTACAGGACCGACTGTGATTCCTCCA
CCACCTCACTCTGCTCCTTCCCTGTTGCCAATGTCTCGCTGACTAAGGGTGGACGTGATCGGG
TGCTGATGTATGGACAGCCGTATCGTGTTACCTTAGAGCTTGAGCTGCCAGAGTCCCCTGTGA
ATCAAGATTTGGGCATGTTCTTGGTCACCATTTCCTGCTACACCAGAGGTGGCCGAATCATCT
CCACTTCTTCGCGTTCGGTGATGCTGCATTACCGCTCAGACCTGCTCCAGATGCTGGACACAC
TGGTCTTCTCTAGCCTCCTGCTATTTGGCTTTGCAGAGCAG

FIGURE 350

AAATTTGAAACCCATAAGTTACCAAGTCTATATCAGGNGCAGTGGCTTTGATTAAAGCCCATT
TTTAAAACTTAAAAACTCAACNCNTCCCAGATTATAATAGAAAAAGAAATGGCNTCAGTTTGA
TCTCGTTCAGAATGCCCCAGATTGTTCTGCTTTGGGGCAGCTGTTTAGTTCAGAGTTATATTN
CAGAGAATTATTTTCTGAGATAATCTTAAACTAGAATGTTCAAAACTAATTGATAATTGAAGT
ATCAAGATACGTAGAACACCTCAGAGATTTTTCTTCAGGAACTTCCACAAACTTTGAATCCTT
GTATCTTTATTTGGTATTCATACTACTAGTAGCAAAATACAGGTTTTTTGTTTTGTTTTGTTT
TGTTTTGGCTTCATAGAGTATCTCAAATTGAAACTTTTCTGCACAAAGAATAAAATTAAGGAT
TTTATAAACTCAAATTGGCACCTACTGAATTAAAATACATAAAATCATTTAAATATAATTCAG
CATATGGGAAGTAACATTGCACTAATATGGAAATCACTGCCAGAGACAGTCTATTTTCTTTTA
ATTTGTTACTACTTAGTCACAAA

FIGURE 351

TCAGAAGGGAATGAAATCCNCAGCGGACCTGGCATCAAAAACTTTGGGCAAAGCAATTGAATT
GNAAGCAATAAAACNGACTTTATCAAGTCCTAAATGTACAAGAGAAGAAGAGAAAATCACTTG
ACAATGAAGTTGAAAAGACAGCAAATCTTGTCATTAGCAACTGGAATCAGCAAATTAAGGCCA
AGAAGAAATTAATGGTTAGTACCAAGAAACATGAAGCACTTTTCCAGCTTGTAGAAAGCTCCA
AGCAATCTATGACTGAGAAGGAGAAGCGGAAGCTCCTCAATAAACTGACAAAATCAACTGAAA
AGTTGGAAAAGGAAGATGAAAATTACTACCAAAAAAACATGGCGGGTTATTCTACCAGACTGA
AATGGGAAAACACACTAGAGAACTGCTACCAGAGCATTCTGGAGCTGGAGAAGGAAAGAATTC
AACTTTTATGCAATAACTTAAACCAGTACAGCCAACATATTTCTCTTTTTGGCCAAACCCTGA
CCACATGCCACAC

FIGURE 352

TTTAAAGAAATGGGTAAATACTGAGCCTTTNTGCAACCTTTTTTGGAAGCACCAGCCCNCAGA
AGATTCTGTGACTTGTGTGCTTTTAGGTGCACCCTCAGACNTCTGGCTCAGTACACCTCGGGN
TGATTGAGACTGTTGCCTCAGTCTCTCATTTGGGTTGACATTATTCATTTTAATGAATGAATA
CATTTGTCGCAGAAAGTGGAATTCTCTCATTGTTGAGAGAAAATTCTCAGCTTGAGTCAAGAA
GTTTCCATATTTACCAGAACCTTCTAGCTTTGATGAGCATAATCACTGCTAAAATAATGTGTC
TTCTGAGCAGCTGGGTACCAGTGCCTGTGGCCTGTAGCATTAGTTACTGCCTGAGGGATGGTG
ACTGTTACCGCAGAATGGTGGGCTTCGTTGACTTGTCTTCTCTCCTCTCCCTCTTACCCACTT
CCCGGAGAAACAGGACAGCAGGCACAGCCAGTAACAAGCTGTGGTACGCCTCCCTGGCCCTGG
TGACGCTCATCATGTATTCCATTGCCACTGGAGGCTTGGTTTTGATGGCAGTGTT

FIGURE 353

GTGGGCCAATGCTGTCCAAACTACAGGGGGTTAATGTAAAGCTTGTGNTAACATATGAAAAGT
ATTTAGAAAGAGCTTGGCATGTAGTAACCACTCAATAAAAGTTAGCTACTATTATGAAGTGTT
TTCCAATGGTTTATTTAGAAGCAAAATAGTATCAGTNTAGAAGTCCAGGCTTGTTTTTCTCCC
AAACATGTTTTCACAAGTGCTTCCATGGTCTCCTTCTCCTTTTCTTCTTCCTCTTCCTCTAAA
AACATATTTTGCTGTGTCTGCTTGGTCATCTTTCACTGGGCCAGAGAAAGAATCCCTGAGGGT
TGGACAAGGGGAGCAGCTGAGTTGGTGAGAAAAGGAGCCCAGCAGGTTGAATGCCTCGAACCA
CTGTGATGAGCTCTTGAGCTGGGTGCCAATCAAAGTGAAGCAGTGGGGCTTGCCAGGTGAGAT
GTTAATTTCAGCAGTCACACGTGTCCCTGTCTGGACTCTCCCTAGGACTCTTGACCCTACCCT
GCAGTGGTTTGAAATGGATTTTATTAGGCTTTCATTACATTCTCATATCATTTTTTTCACTTG
GTATCTAAGCTACACGAGAGCCAGTGTAGTGCTTTGTCCTTG

FIGURE 354

CCGGTAACCCATTGGGCCTGGCNTAANAAAGTTTTTTTAAGCCATTAGACGTTTTTAAAGGAA
TTGGNAGATGNCAATTGGGGAAATATTTAAAATTTAAGTAAAATATAAAGCTTCCTTATTTCA
TGTAACCCAGNCAATCTCAGTATACATGATCAGTTGTGTCTGACAGGTAAATCTATTTGAGGC
CTTATCACACGTTACTTTTAAGAACTAGAAAGGAAAAGTCACTGATCTTAAGTATTTATAATA
CTTCATGTGGTCTAATACTTTTTACGTTTTGTTTTGATTCAGATTTAGTCCGGATTCCCGGTA
TCTGGCAGTAGGTTCTAGTGAGAACTCAGTGGATTTTTATGACCTAACGCTGGGCCCCACTCT
TAACAGAATCAGCTACTGCAAAGACATTCCAAGCTTTGTCATTCAAATGGACTTCTCTGCAGA
TAGCAGTTATCTCCAGGTACAGTACCAATACTGTATACCCAGGTGGCAAGTTCTTCTGCTTTT
ACATTTCGTGTTAGTGAATGCATTTAAAGTTCCTGAGCTCCAGAGCTCCAGCTTCTCAACTCC
TCCCTTTGTACCTTCTGACCTACAGCTCCTCTTTCC

FIGURE 355

TCATGGCGGTATACTTTGGCAAGTGGTTATCTTTTAACGGGTTTCATTTTCCCAGTTGTTAAA
TTTACAGTTGGTTAANTAAAAGTTTTTCCCAGTACGANCAGGGCGTAATCANAGATCCNTAAG
TGTTTAGTNCAGGGCATGTGCTTTTTAAAGTGGGNATGGCTATTTACAGATTGGCCTACACTG
TTNTGGTGGGAGCCNTCAGTGACCAAGGAGCAGAGGTACTTGAAACCCACCCTTGAAGCCATN
TGGATGCTCCGTTCATTCAAATCTGGGGTGTTCTAACCCAAAGTAACTGGCCACAGACTGCAA
TGTAAGATACAAATCTTCAGGACCTAGTGTGTGCACATGTTGGCTCTTATATAAGATGGCATC
CTTAGTACTTGTTCTATGTAGAAAAGAATTTGTGGGCTCACAAGTCCCTACAGAGTCTCACAC
TCTCATGGCCAATAAGTATACAGGGATACCCGGAATTAGACAAACACAGATGAGACATTTATT
TCTGTATATGAATTTATTTTATTTATTTATTTATTTTTTGGGACAGGGTCTCGCTCTGTCGCC
CATCCTGGAGTGCGGTGGCCTGGCTCATTGCAAGCTCCGCCTCCCGGGTTTACACCATTCTGC
CTC

FIGURE 356

TTAATTAGATAATTTAAAGTAGCGTTTTTTTCTACAATGTNTGAAGAAGTGACCTACGCGACA
NTCACATTTCAGGATTCTGNTGNAGCAAGGAATACCCGAGATGGAAATAACNTAAGAAAAAGA
GGGCATCCAGCTCCATCTCCCATTTGGCGTCATGCTGCTCTGGGTCTGGTAACTCTTTGCCTG
ATGTTGCTGATTGGGCTGGTGACGTTGGGGATGATGTTTTTGCAGATATCTAATGACATTAAC
TCAGATTCAGAGAAATTGAGTCAACTTCAGAAAACCATCCAACAGCAGCAGGATAACTTATCC
CAGCAACTGGGCAACTCCAACAACTTGTCCATGGAGGAGGAATTTCTCAAGTCACAGATCTCC
AGTCTACTGAAGAGGCAGGAACAAATGGCCATCAAACTGTGCCAAGAGCTAATCATTCATACT
TCAGACCACAGATGTAATCCATGTCCTAAGATGTGGCAATGGTACCAAAATAGTTGCTACTAT
TTTACAACAAATGAGGAGAAAACCTGGGCTAACAGTAGAAAGGACTGCATAGACAAGAACTCCAC

FIGURE 357

CAAAAANAGTGCCCGTCCNGTTGTTGTAAGTGAAGGGACGGCAGTCAGTTGACCCTGCAGTGT
GCAGGCGAGCGCAGGGAGTACGCCATGTCCTGAGAAGGGGCGATTCTCAGGCTNTGGCAGTTA
CAGCTTCTCCTCACCCTGCCGAGCAACCAGGCCACGGGGCTCCGTGCATCGCCACCTAGAGTG
TTACCCTNTTCCTTGTTCACGGAGGTTCTCCGCAGTGTGTGAGAAAGAGGCCCTCTCTCAGAT
GAATGGATAAAGAAAATGCAGGACATATGGGGGGAGGAGCCAAGATGGCCGAATAGGAACAGC
TCCGGTCTACAGCTCCCAGTGTGAGCGACACAGAAGACAGGCAAGAAGAATAAATGTCTCTGG
TGGAACTTTTGCTCTGGTGGAACTGCTTTTCTAGAACTGGTGTTGCAGCATCCCTGGAAGTGT
CAGAGAGCCCTGGGAGTATCCAGGTGGCCCGGGGTCAGACAGCAGTCCTGCCCTGCACTTTCA
CTACCAGCGCTGCCCTCATTAACCTCAATGTCATTTGGATGGTCACTCCTCTCTCCAATGC

FIGURE 358

GGTTCCCTAAAGATTGAAGCTTTTTAAGACTCAGCTTTTGACACATTTACTAATTATACTTAA
TTGTTCCTTGGTGATTTCACCCCCGTGGGTTTGTTTCCCTTGAACTCCACACTCATTACGTTC
AGAGCCTTTTTNTACACTACTTGAATTATTTTTATTTAGGTATATAAAATACTGGTGGCAATA
GCATAAATTCTAAGTGTTAAACTTGATGAAGTAATATTGTACACCTATGTAAGCACTGCCCAG
ACTGATATACATTTACAGCCTAAGGAGGCTTCTTTGTGCTGCTTTGCTATTAATATTCCATTG
CCCAGAAATAGCCCCTCTCCTAATTTCCATAACCAGAGATAAGCTTACATGTTTTTCCGCTTC
ATGTAAATGGAATCGTACGCTGAACCCTTTTTTGTGTCTGGTTTCTTTTGCTCAACATTATTT
CATGCAACAATAAGGATGGCTCTCTCAGACATAATATTCATTTTTATTTATGTAGTGTTTTAT
GGGAATTGCACTGAGTTAGAGAAACTGAAGTNTGAAGGAATAGTTTCCACAAGACTGCCCTCA
TTTCAGAC

FIGURE 359

AGTGCCGTCCCGGTGTTGTAAGTGAAGGACGGCAGTCAGTTGCCCTGCAGTGTGCAGGCNAGC
GCAGGAGTACCGCCATGTCNTAANAAGGGCGATTNTCAGGNTNTGGCAGTACAGTTTCTCCTC
ACCCTGCGAGCAAACCAGGCCACGGGGCTCCGTGCATCGCCACNTAGAGTGTTACCCTCTTCC
TTGTTCACGGAGGTTCTCCGCAGTGTGTGAGAAAGAGGCCCTCTCTCAGATGAATGGATAAAG
AAAATGCAGGACATATGGGGGGAGGAGCCAAGATGGCCGAATAGGAACAGCTCCGGTCTACAG
CTCCCAGTGTGAGCGACACAGAAGACAGGCAAGAAGAATAAATGTCTCTGGTGGAACTTTTGC
TCTGGTGGAACTGCTTTTCTAGAACTGGTGTTGCAGCATCCCTGGAAGTGTCAGAGAGCCCTG
GGAGTATCCAGGTGGCCCGGGGTCAGACAGCAGTCCTGCCCTGCACTTTCACTACCAGCGCTG
CCCTCATTAACCTCAATGTCATTTGGATGGTCACTCCTCTCTCCAATGC

FIGURE 360

CAAAATGTTAAGAACGTCCACTCCTAATCTGTGGGTGGTNTGCATTGCCGGGCCCCNTGGTTN
TCTTNTGGCATTTTNTGCTTNTGCNTCATATTCTTGTTAGGCCAGGTGGGCTTGTTGCAGGAC
ACCCCCAGTGCNTGGATTACGGGCCCCCTTTCCAGCCCCCTTTGCACCTTGAGTTTTGCTCTG
ACTATGAGTCCTTCGGCTGCTGTGATCAGCACAAGGACCGCCGCATCGCTGCCCGGTACTGGG
ACATCATGGAATATTTTGATCTGAAGAGACATGAGCTGTGTGGAGATTACATTAAAGACATCC
TTTGCCAGGAGTGCTCGCCCTACGCAGCCCACCTNTACGACGCCGAAAACACCCAGACGCCTC
TCCGGAATCTCCCGGGCCTCTGCTCTGATTACTGCTCTGCCTTCCATTCTAACTGTCACTCAG
CCATTTCCCTGCTGACCAATGACCGCGGCCTCCAGGAGTCTCATGGAAGGGACGGTACCCG

FIGURE 361

CCCACGCGTCCGGCTTGAAGACTGACAAGATGTCCCTGTGGACTCCCAAACTCTACTCCAGAT
GGGGAGGTGCCCTTAACACCAAGATTTTAAAAGCTCCAATTTCAGAGCAAGAGTCGAAAACTC
ACAGATAAAGTTATAGTTATTTCAGGGTTCTGAAAAGACGCAGAACATGAAGGGACTCAGAAG
TCTGGCAGCAACAACCTTGGCTCTTTTCCTGGTGTTTGTTTTCCTGGGAAACTCCAGCTGCGC
TCCGCAGAGACTGTTGGAGAGAAGGAACTGGACTCCTCAAGCTATGCTCTACCTGAAAGGGGC
ACAGGGTCGCCGCTTCATCTCCGACCAGAGCCGGAGAAAGGACCTCTCCGACCGGCCACTGCC
GGAAAGACGAAGCCCAAATCCCCAACTACTAACTATTCCGGAGGCAGCAACCATCTTACTGGC
GTCCCTTCAGAAATCACC

FIGURE 362

AATCACCCGGGTCGCTGTTCCTNAGGTGGTCAAGGTGGACAGGGGCGGTGGTNATGGCNCAGT
TTGACANTGAATACCAGCGCCTAGAGGCCTCCTATAGTGATTCACCCCCAGGGGAGGAGGACC
TGTTGGTGCACGTCGCCGAGGGGAGCAAGTCACCTTGGCACCATATTGAAAACCTTGACCTCT
TCTTCTCTCGAGTTTATAATCTGCACCAGAAGAATGGCTTCACATGTATGCTCATCGGGGAGA
TCTTTGAGCTCATGCAGTTCCTCTTTGTGGTTGCCTTCACTACCTTCCTGGTCAGCTGCGTGG
ACTATGACATCCTATTTGCCAACAAGATGGTGAACCACAGTNTTCACCCTACTGAACCCGTCA
AGGTCACTCTGCCAGACGCCTTTTTGCCTGCTCAAGTCTGTAGTGCCAGGATTCAGGAAAATGG

FIGURE 363

GTCCGAACCTGAGCAAACACAGCAGCCCGAGTGTTCCCAAGGCCAAAATGCTGAGAACGTCCA
CTCCTAATCTGTGTGGTGGTCTGCATTGCCGGGCCCCCTGGCTCTCTTCTGGCATTCTCTGCC
TCTGCCTCATATTCTTGTTAGGCCAGGTGGGCTTGCTGCAGGGACACCCCCAGTGCCTGGATT
ACGGGCCCCCTTTCCAGCCCCCTCTGCACCTTGAGTTTTGCTCTGACTATGAGTCCTTCGGCT
GCTGTGATCAGCACAAGGACCGCCGCATCGCTGCCCGGTACTGGGACATCATGGAATATTTTG
ATCTGAAGAGACATGAGCTGTGTGGAGATTACATTAAAGACATCCTTTGCCAGGAGTGCTCGC
CCTACGCAGCCCACCTCTACGACGCCGAAAACACCCAGACGCCTCTCCGGAATCTCCCGGGCC
TCTGCTCTGATTACTGCTCTGCCTTCCATTCTAACTGTCACTCAGCCATTTCCCTGCTGACCA
ATGACCG

FIGURE 364

CCCACGCGTCCGTGAACACACAAAGAGCTTATTTTGTTAGGCAAATACACATTAATAAGAATG
CCTAGAAGAGGACTGATTCTTCACACCCGGACCCACTGGTTGCTGTTGGGCCTTGCTTTGCTC
TGCAGTTTGGTATTATTTATGTACCTCCTGGAATGTGCCCCCCAGACTGATGGAAATGCATCT
CTTCCTGGTGTTGTTGGGGAAAATTATGGTAAAGAGTATTATCAAGCCCTCCTACAGGAACAA
GAAGAACATTATCAGACCAGGGCAACCAGTCTGAAACGCCAAATTGCCCAACTAAAACAAGAA
TTACAAGAAATGAGTGAGAAGATGCGGTCACTGCAAGAAAGAAGGAATGTAGGGGCTAATGGC
ATAGGCTATCAGAGCAACAAAGAGCAAGC

FIGURE 365

TGGTTGGGGCCTCCAAGATTAGAATGTTACTAGGGCCAAAANCAGTGGGATTGGTAAAAGAGG
CAATGATACCCCCATGAGAGCNTTCACATNCAGAACCAGNCAGAACTTCAAAGGTTTTGATGA
TANCAATGATGATTTCCTGACAATGGCAGAATGTCAATTCATTATCAAACATGAACTTGAAAA
TCTTAGAGCTAAAGATGAAAAAATGATCCCTGGTTACCCTCAGGCAAAGTTGTATCCAGGAAA
ATCATTGTTGAGAAGATTGCTCACGTCTGGCATCGTGATTCAGGTGTTTCCACTGCATGACAG
TGAAGCCCTGAAGAAGCTTGAGGACACCTGGTACACTCGGTTTGCTTTGAAGTATCAGCCCAT
AGAGAATCACAGATTGGAATCTGCCTATCAGAACCATCTAATTCTGAAAGTTTTAGTGTTCAA
CTTCCTCAATTGCTTTGCCTCACTCTTCTATATTGCCTTTGTCTTGAAAGATATGAAGCTTTT
GCGCCAGAGCTTGGCCACTCTCCTAATTACCTCCCAGATCCTCAACCG

FIGURE 366

ATTTGATTAAATTATGAATGAGTTTTACAAATTCCTTTCAGAGTTTTACTAAGATCACACAAA
TAACAGCTTTNTTATTCAGTGAAAAAGATATTTTATTTCTGATGTTTTATTTGCACTCGTGGA
ATATGTTACCATTAATCAGAAACATCATGGCAACCCCTAAGAATAGACTAAGTTTGTGTTGGC
TGAGGGATTNTATTTGGTTTGCTTTTTTTTTGCTTTGTTATATTTTATTGCTACA

FIGURE 367

GGCTACAACTGCTCAACATGGGAAAAGACATTCCGGGCAGATCGGCTTTTGAAAGCTTAAAGG
GAGCTTGATGCTGGCAATGGGATCAGAGTGTTTGACNTGACATCGGGATGTTCATTGCTAGTC
TGACCATCTGGCTCCTCTGTANAAACATTGTTCAGAAACCTGTGACAGACGAAGCAGCACAGA
GTAACCCGGAGTTTGAAAATGAAGAATTGGCTGAAGGAGAAAAAATTGATTCAGAAGAGGCNC
TGATCTATGAAGAGGATTTCAATGGAGGAGATGGTGTTGAAGGCGAGTTGGAAGAAAGCACGA
AGTTAAAAATGTTCCGCAGGCTTGCCTCTGTGGCCTNTAAGCTCAAGGAGTTCATTGGCAACA
TGATCACCACTGCTGGGAAAGTCGTTGTTACCATCTTACTGGGCTCCTCGGGCATGATGTTGC
CGTCTTG

FIGURE 368

TTAAGCCGGAAAATCCCCTTGAACCCAGAAGCGGAAGGTNCAGTCACCCAAAATGGNGCCCAT
TGCATTCCAGCCTCGGTNCGGAGCAAGACTTTGTTTAAAAAAAAAATTTAAATTAGCCATTAC
CCCTAGNTAATTTTTAAATTTTTTGTGAANANAGGGCCTCACTGTCTTGCCCAGGCTGGTCTC
GAACTCCAGGCTTCAGGTGATCCTTCTGCCTTGCCTCCCAAAGGGCGGGATTACAGGTGTGAG
CCACTGTGCCCAACTCATTACTTTTTTAAAAAATTACTTTCCATTTCTAGTTTATATATGACA
GGTACTTACTTTAAGTAGTAAATATTATGTTTAACAATAAATAAAAATGATCAGGATTTCCCC
CGACATGCTTTCCTTTCTTCTCTTTTTCTTCCTTTCTCTCTCATTTTATCCCTTCTCCTGCCC
TTTTTGGAAGTCCTTATTGGAGGAAAAAATAACTTGCCCTATTTGTTTCCTCACTAATTGTTA
TCAGTCTCGGGTATCAAGGCAAGCAGATTCAAATTGCTGTAATATATACAGTGCAATTAGATT
AGAGTCTACTAAGAATTTAATTGGAGAATGTTCAAAATACTTTTCTAAAGTTAATTTTTTTAG
TATTCA

FIGURE 369

TAGAAGGTCCGTCATGGACCCCAGATCCATTTCNTAGNAAGGCCGTCATGACACCCNGGATCC
ATTTCCTAGNAGGGCCGTCATGACACCCCGGATCCTTTTCCCCTCAGAGGGGCTNGTCATGAC
TCAGACACATCTCCTCCCAGAGGATCCGTCATGACTCCTCAGACACTTCACCCCCAAGGAGGG
CCCGTCATGATTCTCCAGATCCTTCTCCCCCAAGGAGGCCTCAGCATAATTCTTCAGGTGCAT
CTCCTAGGAGAGTCCGTCATGATTCACCAGATCCCTCTCCTCCTAGGCGAGCCCGTCATGGTT
CCTCAGATATCTCTTCCCCCAGAAGGGTCCATAACAACTCCCCTGACACATCTAGGAGGACTC
TTGGCTCTTCAGACACACAGCAACTCAGAAGGGCCCGTCATGACTCCCCTGATTTGGCTCCTA
ATGTCACTTATTCCCTG

FIGURE 370

CGGANGCGTGGCCGAACGCNTGGTCCAACCATATGCCAGGTTCAACNCGGATAAAAGTTAGGA
AACGTAACCAGCTTCATTTTTTTGNCAGCAGACTTAAAGATCTGAAACTTGGAACTAATATCA
AGGATTTATGTGCTGCTCTTTGGATTCTGATGAAGAATCCAGTGCTCATATGCCTAGCTCTGT
CAAAAGCTACAGAATATTTAGTTATTATTGGAGCTTCTGAATTTTTGCCTATATATTTAGAAA
ATCAGTTTATATTAACACCCACTGTGGCAACTACACTTGCAGGACTTGTTTTAATTCCAGGAG
GTGCACTTGGCCAGCTTCTGGGAGGTGTCATTGTTTCCACATTAGAAATGTCTTGTAAAGCCC
TTATGAGATTTATAATGGTTACATCTGTGATATCACTTATACTGCTTGTGTTTATTATTTTTG
TACGCTGTAATCCAGTGCAATTTGCTGGGATCAATGAAGATTATGATGGAACAGGGAAGTTGG
GAAACCTCACGGCTCCTTGCAATGAAAAATGTAG

FIGURE 371

AATAAAAAATGGCTTAAAAGAACATTTCCGAACCAAAAGGAACCGGTTCCNGCCTTAACAAAG
TGGGACATTGGCCNTCAAAGGGGNCCTCATGGGAACATCNTGTTTTGCGGGGGCANGCACAAT
GGTCAAGGGCTTCCCTAACCGTTTGCANAAGNAGTTAANCAGCATGTGTCCCAATGNCCCCCG
CAGGTAAACGTGCTGCCTGAAANAGCCAGTCCGTGTGGACCGGGGCTCCATCCTGGCCTCATT
CAGGGTTTCCAACCATTGTGGGTCCACCGCTTTGAGTACGAGGAACACGGGCCTTTCTTCCTC
TACAGAAGGTGTTNTGAACGGCGACAACTTTGGCGTCGTGAGATTCTTGTGAGGCGTCTGCCT
GGAAGCCGGCAGCAATTTTTGCTTCTTTAAAGAGAAAAAGAAGGCTAGGGACTCAGATTCCTG
GATTCTGAGATCCAGACCAGCTCCTCCCAGACCTNTCCAGAAGAAGCCATGGGAACCCCTCGT
ATCCAGCATTTGCTGATCCTCCTGGTCCTAGGAGCCTCCCTCCTGACCTCGGGCCTAGAGCTG
TATTGTCAAAAGGGTCTGTCCATGACTGTGGAAGCAGATCCAGCCAATATGTTTAACTGGACC
ACAGAGGAAGTGGAGACTTGTGACAAAGGGGCACTTTGCCAGGAAACCATACTAATAATTAA

FIGURE 372

GTGCGCATAAAGAGGAGGCGCTTGCCTTCAGCTTGTGGGAAATCCCGAAGATGGCCAAAGCAA
CTCAACTGTTCGTTGCTTCCAGGGCCTGCTGATTTTTGGAAATGTGATTATTGGTTGTTGCGG
CATTGCCCTGACTGCGGAGTGCATCTTCTTTGTATCTGACCAACACAGCCTCTACCCACTGCT
TGAAGCCACCGACAACGATGACATCTATGGGGCTGCCTGGATCGGCATATTTGTGGGCATCTG
CCTCTTCTGCCTGTCTGTTCTAGGCATTGTAGGCATCATGAAGTCCAGCAGGAAAATTCTTCT
GGCGTATTTCATTCTGATGTTTATAGTATATGCCTTTGAAGTGGCATCTTGTATCACAGCAGC
AACACAACGAGACTTTTTCAC

FIGURE 373

TTTAAGGATGTTGCCATGNACCATGTTTTTTCAAATTTGCTTTTCATTTGGGNCCGTTTTGGA
GTCTTTGACCGCTANGATGGTTTTCGTCGTCTGGGAACTTGATCAGACTTTGAAGATTNTAAA
TTTGGAAGATCAGGGTGCACTTTTGAGTGATGATGAAATATTTGTAGCCGCCAAATTGGGAAA
CATACCTGCATGGCCTTGCGCAAATACTTTGAGGCTCACCTGGCCATTAAATTGGAACAAGTG
AAGCAGTCACTTCAGAGGACTGAGGGTGGCATTNTTGTCCACCCACAACCCCCGTACAAGGCA
TGCTCATATACTCATGAACAGATTGTGGAAATGATGGAATTTTTGATAGAATATGGCCCAGCG
CAGCTATATTGGGAACCAGCTGAAGTTTTCCTCAAACTTTNTTGTGTGCAACTCTTGTTGCAG
CTTATTTNTATTGCCTGCAATTGGAAGACCTATTATGCAAGGAATGACACTGTGCGCTTTGCT
TTGGATGTCCTGGCTATTCTTACTGTGGTGCCAAAAATCCAGCTCCAGTTGGCAGAATCAGTG

FIGURE 374

AAATTTTTTAAAAAAACTCCTTAATAGGCCCTTTTTTTTTTTAACCTGAAAGTTGACTACCTA
CCTTTCAGGAAATATATATTTTTTGGGTTTAGCTAGGTTGACTTTCTTCTAGAAATGGAAAAG
ATGGCACCCTCGGTACCAAAGTGCTGGGACTCTGCACTATGCTTGTGTGTATGTGTGTGCCTC
TGTCTTGCTCTCTTATCTCCCAGCAGTGAGACATTGGACGTGTTTGCTCATGAAGATGCAGTA
TATGGCTTGTCTGTGAGCCCAGTGAATGACAACATTTTTGCCAGTTC

FIGURE 375

TTTTTTTGGGAGGAGGAATGTNCATTCAGGGAGTAGCTTTTTGGGAAAAATTNTNTAGGGCTA
CANACAGTCATGGGTGACTTTCTTTCTGCTGTGAAAACTCCCAGAGTNTCTTTAGGGATTTTC
CCTAAGGTGACCACCAGGCACACCTCAGTNTTTTGACCCAGAGCCTGAAAACTGTTTTCANT
GGGTTCCACCAGTCCCAGCAAAATCCTCTTTGTATTTATTTTGCTAAGTTATTGGGGTTTTGC
TTACATCTCATGATTGATATAATACCAAAGTTCTATAGCCTTNTCTTGCAGTATTTGGATTTG
CTTGAAACCGGGAAAACTGTTCCCATTAGGCTTGTTAATGTCAGAGTGACACTATTATGAATC
TTTCTCTCCCTTTCCTCGGCCTGTTTCTTCTCTCTTTCTCCTTCAAACTTGCTCTGCAGCTAA
GGAAGGTGAGTCTACTTTCCCTGAGGCTTTGGGGTCAGAGTATATGTTGTTTGGAGAAAGAGG
GCAATCAGGACTNTTCTGGGACCCAGATGAGTTCTTCACTAGCCCTTNTGAA

FIGURE 376

AAATGTTACCCTATCCTCGGANAAGGGTTTGAATCCCNCTGATGTGTGTGGATCCATTTTGGT
GGTGNCAATGATTCTCTCGTCCTATTTTATTAACTTCATCTACCTTGCAAGAGCACAAAAAAA
CCATGCTAACTTTAACTTTGGATGTGCAATTACATTCCTCCTTGTTGCAGGGACATTTTTTCC
ANANAGNTCCAATCCTGGTTAATCCGAAGCCAAAGAGAGTGTTTCTTCAGCATATGACTAGAA
CATTCCATGACTTGGAAGGAAATGCAGTTAAACGGGACTCTGGAATATGGATCAATGGGTTTG
ATTATACTGGAATTTCTCACATAACCCCTCACATTCCTGAGATCAATGATAGTATCCGAGCTC
ACTGTGAGGAGAATGCACCTCTTTGTGGTTTTCCTTGGTATCTTCCAGTGCACTTTCTGATCA
GGAAAAACTGGTATCTTCCTGCCCCAGAAGTTTCTCCAAGAAATCCTCCTCATTTCCG

FIGURE 377

TTTGACTGGGTGTAAGAATATGCTGTTCCAGCAGACCAAGGATGGCATTGGGAAATCTGCNTN
TGGGGTAGGCACATCTTCATGGGCTATTTGGAAAGTGAGACTTGAAACTACAGAGGCCATCGA
TGATGAAGGCTGGTTACACTCTGGGGATTTGGGCCAGCTGGACGGTNTGGGTTTCCTCTATGT
CACCGGCCACATCAAAGAAATCCTTATCACTGCTGGTGGTGAAAATGTGCCCCCCATTCCTGT
TGAGACCTTGGTTAAGAAGAAGATCCCCATCATTAGTAACGCCATGTTAGTAGGAGATAAACT
GAAGTTTCTGAGCATGTTGCTGACGCTGAAGTGTGAGATGAATCAGATGAGCGGAGAACCTCT
GGACAAGCTGAACTTCGAGGCCATCAACTTCTGTCGGGGTNTGGGCAGCCAGGCATCCACCGT
GACTGAGATTGTGAAGCAGCAAGACCCCCTGGTNTACAAGGCCATCCAGCAAGGCATCAATGC
TGTGAACCAGGAAGCCATGAACAATGCACAGAGGATTGAAAAGTGGGTCATCTTGGAGAAGGA
CTTTTCCATCTATGGTGGAGAGCTAGGTCCAATGATGAAACTTAA

FIGURE 378

GTGGAGGAAGAAGACATTATACAAAACAAATTTAGAAACTGGGATCATGAGTGGAAAAACAAA
GGCAAGAAGGGCTGCCATGTTTTTTAGACGTTGCTCTGAAGACGCCAGCGGTAGCGCCAGTGG
CAATGCTTTGTTATCAGAGGACGAAAATCCTGATGCGAATGGGGTAACTCGATCATGGAAGAT
TATTNTAAGTACAATGCTTACACTGACTTTTCTTCTTGTAGGACTCCTAAATCATCAGTGGCT
TAAAGAAACAGATGTTCCTCAGAAATCCAG

FIGURE 379

AGCCAAAATCCTTGGCCAAATTTNGCATTTCCAANTCCGGAGGCCAAGAAAGGAAGAAAGTTC
CCCAGGTNGAAAANCAAACTTGGATTTTCAGCAATATGGATTTATTAATCAAATGTGGTTACC
ATTTGGGCCCTTCCGGGGGATTTTAAGTACTTTTCCATACCTAGCTNTTATACATACTATTAT
TCTCATGGCAGTAGCAACTTTTGGTTCAAATATCCCAAAACATGCTCAAAAGTAGAACATTTT
GTTTCAATATTAGGAAAGTGCTTTGAATCCCCTTGGACGACAAAAGCGTTGTCTGAGACAGCA
TGCGAAGACTCAGAGGAAAACAAGCAGAGAATAACAGGTGCCCAGACTCTACCAAAGCATGTT
TCTACCAGCAGTGATGAAGGGAGCCCCAGTGCCAGTACACCAATGATCAATAAAACTGGCTTT
AAATTTTCAGCTGAGAAGCCTGTGATTGAAGTTCCCAGCATGACAATCCTGGATAAAAAGGAT
GGAGAGCAGGCCAAAGCCCTGTTTGAGAAAGTGAGGAAGTTCCGTGCCCATGTGGAAGATAGT
GACTTGATCTATAAACTCTATGTGGTCCAAACAGTTATCAAAACAGCCAAGTTCATTTTTATT
CTCTGCTATACAGCGAACTTTGTCAACGCAATCAGCTTTGAACACGTCTG

FIGURE 380

CGGATCCTTTAAAATCCCTGACCTNGACCCAAGGGTCCGGTAAAATCAATTTGTNTTACCCAA
AGACCAATTTTTGACATATCTTGAATAGGATGNCTATAAATTATGACTTTTAAATTGTTGTAA
TTTTTGTACTATTATCTGANATTTTTATTTTTATGNATTTTCGTAAGTAGTTTAGAGATAGTC
ACATTTTAAAAATCTAAGATCAAGCAAATGAAGCTTATTTTTATGTATTCATAGTATAAAAGC
CTTCAGTAAATAGGTAATATTTTTGTTTTATTCTAGAAAACAGCTCCTTGAACACAGTGAGCT
GGCTTTTCACACATTGCAGTTGTTAGTGTTTACTGCCCTTGCCATTTTAATTATGAGGCTAAA
GATGTTTTTGACACCGCACATGTGTGTTATGGCTTCCTTGATATGCTCTCGACAGCTCTTTGG
CTGGCTTTTTCGCAGAGTTCGTTTTGAGAAGGTTATCTTTGGCATTTTAACAGTGATGTCAAT
ACAAGGTTATGCAAACCTCCGTAATCAATGGAGCATAATAGGAGAATTTAATAATTTGCCTCA
GGAAGAACTTTTACAGTGGATCAAATACAGTACCACATCAGATGCTGTCTTTGCAGGTGCCAT
GCCTACAATGGCAAGCATCAAGCTGTCTAC

FIGURE 381

GAATAAGTTGGGATTTTTNAGCAAGGATTCCAATNTGATTCTTAAAAAAGGAGTTAGCCATAA
AGCCAGTGGTTTTAATTAGATTCAGATTTGATTTTTAAATTTTACGGGTTTCAGNTTCAGGGA
ATGCTACCCNCAAAATGAGATTTCATTACTATATACCAGTGAAATTTCTACTCTCANATTTTC
TGTAATGTCATTTTTCATAGTTAGGTTTTAGAAAGTATCTAATCAGGTTGTGATGGTCAAATA
AAGGGTTCAAACACATTTCTATTTTCTGNTTCAATAAATATTTTTTATATTGCTTATTCTTAT
CTATCTTTACCTAATTTCTTCCTATCTTTTTCGNTAACTTTCTTTTTTTTTATTTTCTTCTAA
TGAAGATTCTGCTTTCTTCATCTAAACCTGTCCCAAAAACCTATGTACCAAAACTTGGCAAGG
GTGATGTAAAGGATAAGTTTGAAGCCATGCAGAGAGCCAGGGAAGAAAGAAATCAAAGGAGAT
CTAGAGACGAAAAACAAAGAAGAAAAGAACAATATATTAGAGAGAGAGAATGGAACAGGAGAA
AGCAGGAGGTTATTTTATTTTACTTTATTCTCGTGAAAATATTTGTTTGCATTTTTTCATTTA
AATTGTATTTATTCACATTAAC

FIGURE 382

GTCCATGGAGCTGGTGGTCAAGGTGGACAGGGGCGGTGGTGATGGCGCAGTTTGACACTGAAT
ACCAGCGCCTAGAGGCCTCCTATAGTGATTCACCCCCAGGGGAGGAGGACCTGTTGGTGCACG
TCGCCGAGGGGAGCAAGTCACCTTGGCACCATATTGAAAACCTTGACCTCTTCTTCTCTCGAG
TTTATAATCTGCACCAGAAGAATGGCTTCACATGTATGCTCATCGGGGAGATCTTTGAGCTCA
TGCAGTTCCTCTTTGTGGTTGCCTTCACTACCTTCCTGGTCAGCTGCGTGGACTATGACATCC
TATTTGCCAACAAGATGGTGAACCACAGTNTTCACCCTACTGAACCCGTCAAGGTCACTCTGC
CAGACGCCTTTTTGCCTGC

FIGURE 383

GGATGGGAAGGATCGATTAAAGGATTGGCTTTTGGAANACTTACTGGTGGGAATAAGGTTGGC
CTTGTGCAAAGTCCCCAAGGCNTGACATTAGTTTGCTGGCAAGGCAATTGATTCCTCNTTTCA
ACATCGCTTATGCAGCTTTCTGTTCTTCGGTAATCTATGAATTTTTGGATCGTGTCATCAAAT
GTCCATTGGTTCCTTCTTCCTGGTGAGTGCTCTGCTGATCAACGTTCTGAAAGTGAGCCCATT
CAACAACGGTCAACTGGTCATGGGATCTTTCGTCAAGAATGAGTTTTCGGCCCCCTCCTACCT
TATGGGCTATAATAAATCCTTGAGTGTGGTGGCAACCACAACTTTTCTGACTGGGATTATTCA
GCTAATAATGGGCGTATTGGGTTTGGGCTTCATTGCCACTTACCTTCCGGAGTNTGCAATGAG
TGCTTACCTGGCTGCTGTGGCACTTCATATCATGCTGTCCCAGCTGACTTTCATCTTTGGGAT
TATGATTAGTTTCCATGCCGGTCCCATCTCCTTCTTCTATGACATAATTAATTACTGTGTAGC
TCTCCC

FIGURE 384

TGTTTATGTCACCTACCTTCNCCTTTTTAAGTTTTGTCCNAGCAAACCTTGCAGAATTTTAGA
TGAACATGGNAAAAATGTTACAATCTGTGGGCCTGACTTTGGTCAAGACCTGTACANAGATGA
AAACTTGGTGACTATACTGGGGACCAGCTTCTTAATCGGATGTATCTTGTATTCATGTTTGAC
ATCAACAACAAGATCGAGTTCTGACGCTCTGCAGGGGCGATACGCAGCTCCTGAATTGGAGAT
AGCTCGCTGTTGTTTTTGCTTCAGTCCTGGTGGAGAGGACACTGAAGAGCAGCAGCCGGGGAA
GGAGGGACCACGGGTCATTTATGACGAGAAGAAAGGCACCGTCTACATCTACTCCTACTTCCA
CTTCGTGTTCTTCCTAGCTTCCCTGTATGTGATGATGACCGTCACCAACTGGTTCAACTACGA
AAGTGCCAACATCGAGAGCTTCTTCAGCGGGAGCTGGTCCATCTTNTGGGTCAAGATGGCCTC
CTGCTGGATATGCGTGCTGTTGTACCTGTGTACGCTGGTCGCTCCCCTCTGCTGCCC

FIGURE 385

AACAGGGGGGCCGCTTGNTCCAGAAATGTTTCCCCTGGGGAAAGTGGCATCACTTAATGACAT
TCAGCCAACTTACNGAATCCTGAAACCATGGTGGAATGTGTTTATGGATTACCTAGCTGTTGT
TATGTTAATGGTAGCCATCTTTGCAGGAACCATGCAACTTTACCAAAGATCAGGTGGTCTGTT
TGCCAGTATTGCCATCTCCTGTAAATTCAAAGGCACATACACCACCAGGAAATGCCGAGGTCA
CCACCAACATCCCAAAGATGGAAGCAGCCACCAACCAAGACCAAGATGGGCGGACAACAAACG
ACATTTCCTTTGGGACATCTGCTGTGACACCTGACATACCTCTCAGAGCCACATATCCTCGCA
CAGATTTCGCACTTCCAAATCAGGAGGCAAAGAAAGAGAAGAAAGATCCAACAGGTCGAAAAA
CAAACTTGGATTTTCAGCAATATGTATTTATTAATCAAATGTGTTACCATCTGGCCCTTCCGT
GGTATTCTAAGTACTTTCCATACCTAGCTCTTATACATACTATTATTCTCATGGTCAG

FIGURE 386

ATCAAGTTGGTGAAGAAAGAACCTATGAAATCTGTACAAAAGATTGGGGCTTTGTTCTTCCTG
TTAAGTGGTGTACTGGTGATGACCGGAAGCATGGCCTTGATTGTTTTGGATTGGGTACACAAT
GCACCTGGAGGTGGCCATTAATTGGCACCACTCAAACTCAAACTCAGTCCATCTGATGCCAGT
GTTGAGTAAACTCAACTACTATGAAATTTCACCTAATGTTTTCAGTTTCACTTCCTTTTGAAG
TGCAGATTCCTCG

FIGURE 387

TGGATTTAATGGGGGGAAAGGGCGGAAAANGGNCAAGGATCCAAACTGGNGAATTTGGTGATT
TTCGGGTCCCTNTCCGCTTTCCGGCCGGNCAGCGCTGCCAAGGGTATATTTCCTTTTTTCNGA
TCCTGCAACAAGCCTCTTTAAACTGTTTAAATGAGAATGTCCTTGGNTCANAGAGTACTACTC
ACCTGGCTTTTCACACTACTCTTCTTGANCATGNTGGTGTTGAAANGGATGAGAAAGNCCTTG
GACTGGTTCCTCATATTCATTCCAGTTGGAAANTTGANACTATCCTTCTTGTCCTGCTGATTG
TGAAAATGGNTGGGCGGTGTAAGTCTGGCTTTGACCCTCGACATGGATCACACAATATTAAAA
AAAAAGCCTGGTACCTCATTGCAATGTTACTTAAATTAGCCTTTTGCCTCGCACTCTGNGGTA
AACTGGAACAGTTTAC

FIGURE 388

GTTAGGTGATCCAGGTTTTGGGGTTTTTGCAACCCTTGGGGTCATTGGGCCCTTNAAATTAAT
CTTCGGGGGGGGTCCTNGCCATGGNCAGCCAAACATTTTTGGGNACATACCATTTGGTTCTGT
AATCGGGGCGTTTTCAGTTTCCTGTGTAAAGGGCNTGGGCATTGCTATCAAGGANCTGTTTGC
AGGGAAGCNTGTGNTGCGGCATCCCCTGGNTTGGATTCTGCTGNTGAGCCTCATCGTCTGTGT
GAGCACNCAGATTAATTACNTAAATAGGGCCCTGGATATATTCAACACTTCCATTGTGACTCC
AATATATTATGATTCTTTACAACATCAGTTTTAACTTGTTCAGCTATTCTTTTTAAGGAGTGG
CAAGATATGCCTGTTGACGATGTCATTGGTACTTTGAGTGGCTTCTTTACAATCATTGTGGGG
ATATTCTTGTTGCATGCCTTTAAAGACGTCAGCTTTAGTCTAGCAAGTCTGCCTGTGTCTTTT
CGAAAAGACGAGAAAGCAATGAATGGCAATCTCTCTAATATGTATGAAGTTCTTAATAATAAT
GAAGAAAGCTTAACCTGTGGAATCGAACAACACACTGGTGAAAATGTCTC

FIGURE 389

AAAAAAAAAAAAAAAGAATNTGACTATATACCATGGAAAAGCCNCCACTNTGCCACTTAAATA
AACATCAGGATCAGAGATTCCAAGAGGACAATNTGCATCAAGTNTTCACCAAGTGTTTTTTAA
GCGAAATAATGAAATAGGGAGCAGAATATGCCTGTTGCCCATAGAAACGAGGTNTATTNTTGT
CCTCAATTAGGCTTTTTTTTTNTTCATAGTTACACCAGAACTAAAGTAAAAGTGGTTTTTCTG
TTCTTTCTACTTCTCCCCATGAAATGGGCATATCATNTCAACACTTCACTCCAAGTCGCCACG
GGCAACCTTATGACCCTAGGTCCTCCACCCCTAATGTATCATCATTGCCA

FIGURE 390

AGGGCGCCCATTTCGAGCCCAAGTTTCCAGTTCGGGTTTCCGGGCTCAGAATTTTCCAGGAGT
GGGTTCTTGGGCAGTGGCTGTGGAGCAGGAATGGCGCAGTAGAGGGTTACTGTTTCTCGGCCG
CCTTGAGCTGTACCTTTTTAGTGTCCTGCCTCCTTTTCTCCGCCTTCAGCCGGGCGCTGCGAG
AGCCCTACATGGACGAGATNTTCCACCTGCCTCAGGCGCAGCGNTACTGTGAGGGCCATTTCT
CCCTTTCCCAGTGGGATCCCATGATTACTACATTACCTGGCTTGTACCTGGTGTCAGTTGGAG
TGGTCAAACCTGCCATTTGGATCTTTGGATGGTCTGAACATGTTGTCTGCTCCATTGGGATGC
TCAGATTTGTTAATCTTCTCTTCAGTGTTGGCAACTTCTATTTACTATATTTGCTTTTCCACAA

FIGURE 391

CCAGTTTTTCATGGACATAGAAAATTCCAAAAGAATAATAATATTGAATTTAAATTTGGGGGG
GTTAAAAAAANAAAACTTAACTTTATAAAATTATTTATTNTATTTTAAGCCTTNTATCATATT
TTCCCCATCCAATTGTTTGGTTTCAGTGGTCCAGCTTTTATTTACAGGCATATAAAAGAAATT
GTGAGATGTTTTGCAAGCTTTTTTTTACTTTGAGAGCTTTTAATTTGTATGTTTTTATGTGGA
TGAAGAGCATTTTTTATGTTTTTGTGCAATAGGTTCCAATATGCATTTATTAGACATCTGTTT
AAATGGTAATGTAGCATTTATTTTGCTAAATTGAAAGGGAACATAGATGGAATTCCAAAATAT
GTACATTCAGCTGTTTGGTTTTTCGTTTTTCATTGTTATTATTGTGAGAATGCTGTTATTGGG
GTTGTGTGTGAGTGCCCGTCAGCCAGTGATGCCTCGGGCCACGCTGTGGGGCCACCTCAGTCC
TGCTGGGTCCTGGTGCCTTGGACCCCACGTGCTTGTGGCCAGGCTGCCCCTGGGCGGGGCCAT
GTGGCCTCAGACCACAAGAG

FIGURE 392

CGTCTCCAGTCTACCTCCGAGAGATTAGCTGAAACACAGAATATAGCGCCATCATTCGTGAAG
GGGTTTCTTTTGCGGGACAGAGGATCAGATGTTGAGAGTTTGGACAAACTCATGAAAACCAAA
AATATACCTGAAGCTCACCAAGATGCATTTAAAACTGGTTTTGCGGAAGGTTTTCTGAAAGCT
CAAGCACTCACACAAAAAACCAATGATTCCCTAAGGCGAACCCGTCTGATTCTCTTCGTTCTG
CTGCTATTCGGCATTTATGGACTTCTAAAAAACCCATTTTTATCTGTCCGCTTCCGGACAACA
ACAGGGCTTGATTCTGCAGTAGATCCTGTCCAGATGAAAAATGTCACCTTTGAACATGTTAAA
GGGGTGGAGGAAGCTAAACAAGAATTACAGGAAGTTGTTGAATTCTTGAAAAATCCCGAACCC
CTT

FIGURE 393

GGTCAAGTTCAGTAGTGGTCTCAATAAGTGTGTTAAACTTGCTTTGGGTGATTGCAATCAGCA
TGGGATTTGGCCATTTCTATGGCCCAATTCANATTCAGAAGCGTCNACAGTTAGTCAGAAAGA
TACATGAAGATGAATTGAATGATATGAAGGATTATCTTTCCCAGTGTCAACAGGAACAANAAT
CTTTTATAGATTATAAGTCATTGAAAGAAAATCTTGCAAGGTGTTGGACACCTANTGAAGCAG
AGAAGATGTCCTTTGAAACTCAGGAACCCCTT

FIGURE 394

GCAGTGGGTGATCATAGGCACTAACCCTCAAACTCCTGAAGTTCAANAGATTGTCCCATGTCA
GCCTCCCAAGTAGCTGGGACTATAGACAGGNGCCATCATGCCCAGCTAATTATTTTTTTAATT
TTANAGAAGAGTCTTGCTAGGTTCCCCAGGCTGGTCTCGAACTCCTGACCTCAAATAATCCTC
CCNCCCTCAACCTCTGAAGTAGCTGCAATGACAGGTGCAAGCCCACTGTGTTTGGCTAGAGTC
TCATGTTTTTCTAATTCCAAAAAAGTTCCATAATGATTTTGATTCAGATTGTATTGAGTTTAC
ACATTAATTTAAGAAGTGACATCTTCATAATACTAACTTTCCCCAAAAAGAAACAGGGTATGT
TTTTCCATTTATATGAGTGGGGTTTTTTTTGTTTTGTTTTTACGTTTTGTAGTTTTCTTCATA
TAGGTTTTGCCAGAGGTTCCCAAACTTTCTTGGTTCATGG

FIGURE 395

AGCATGGGAAAGGTAGGAACCNAGGGAAAGGGGCCCCCCGAGCGCAAGGTGTCGGTGCCCACC
TTCAGNTGGAGGAGATTCAAAAGCATAACCTGCGCACCGACAGGTGGCTGGTCATTGACCGCA
AGGTTTACAACATCACCAAATGGTCCATCCAGCACCCGGGGGGCCAGCGGGTCATCGGGCACT
ACGCTGGAGAAGATGCAACGGATGCCTTCCGCGCCTTCCACCCTGACCTGGAATTCGTGGGCA
AGTTCTTGAAACCCCTGCTGATTGGTGAACTGGCCCCGGAGGAGCCCAGCCAGGACCACGGCA
AGAACTCAAAGATCACTGAGGACTTCCGGGCCCTGAGGAAGACGGCTGAGGACATGAACCTGT
TCAAGACCAACCACGTGTTCTTCCTCCTCCTCCTGGCCCACATCATCGCCCTGGAGAGCATTG
CATGGTTCACTGTCTTTTACTTTGGCAATGGNTGGATTCCTACCCTCATCACGGCCTTTGTCC
TTGC

FIGURE 396

AATGGTACAACAGTCCCTTAATGGTTGCCNCAATGGCNTGAAATCCAAGNATTACAGACTTTT
GTGATAAGGTNAAGCTTGGGGCATCGTCCTAGAAACGGTGGCCACAAGTGGGGTTGTGACCTC
GGTGGCCTTCATGCTCACTCTCCCGATCCTCGTNTGCAAGGTGCAGGACTCCAACAGGCGAAA
AATGCTGCCTACTCAGTTTCTCTTCCTCCTGGGTGTGTTGGGCATCTTTGGCCTCACCTTCGC
CTTCATCATCGGACTGGACGGGAGCACAGGGCCCACACGCTTCTTCCTCTTTGGGATCCTCTT
TTCCATCTGCTTCTCCTGCCTGCTGGCTCATGCTGTCAGTCTGACCAAGCTCGTCCGGGGGAG
GAAGCCCCTTTCCCTGTTGGTGATTCTGGGTCTGGCCGTGGGCTTCAGCCTAGTCCAGGATGT
TATCGCTATTGAATATATTGTCCTGACCATGAATAGGACCAACGTCAATGTCTTTTCTGAGCT
TTCCGCTCCTCGTCG

FIGURE 397

GACCTCGACCCCAGGGTCCGGTTNTACTTTGTCCTGCCTGCTGCTGGGGTCCCTGGGTCTATG
TGCATCCTCTTCACTATCTACTGGATGCAGTANTGGTGTGGGGCTTTGCCTGGAATGGCAGCA
TTTACATGTTCAACTGGCACCCAGTGCTTATGGTTGCTGGCATGGTGGTATTCTATGGAGGTG
CGTCACTGGTGTACCGCCTGCCCCAGTCGTGGGTGGGGCCCAAACTGCCCTGGAAACTCCTCC
ATGCAGCGCTGCACCTGATGGCCTTCGTCCTCACTGTTGTGGGGCTGGTTGCTGTCTTTACGT
TTCACAACCATGGAAGGACTGCCAACCTCTACTCCCTTCACAGCTGGCTGGGCATCACCACTG
TCTTCCTCTTCGCCTGCCAGTGGTTCCTGGGCTTTGCTGTCTTCCTCCTGCCCTGGGCGTCCA
TGTGGCTGCGCAGCCTCCTAAAACCTATCCACGTCTTTTTTGGAGCCGCCATCCTCTCTCTGT
CCATCGCATCCGTCATTTCGGG

FIGURE 398

AGAGGAGCTGCCGGTGCCTCCTCAGAACATCTCCTGATCGCTACCCAGGACCAGGCACCAAGG
ACAGGGAGTCCCAGGCGCACACCCCCCATTCTGGGTCCCCCAGGCCCAGACCCCCACTCTGCC
ACAGGTTGCATCTTGACCTGGTCCTCCTGCAGAAGTGGCCCCTGTGGTCCTGCTCTGAGACTC
GTCCCTGGGCGCCCCTGCAGCCCCTTTCTATGACTCCATCTGGATTTGGCTGGCTGTGGGGAC
GCGGTCCGAGGGGCGGCCTGGCTCTCAGCGTGGTGGCAGCCAGCTCTCTGGCCACCATGGCAA
ATGCTGAGATCTGAGGGGACAAGGCTCTACAGCCTCAGCCAGGGGCACTCAGCTGTTGCAGGG
TGTGATGGAGAACAAACTATGTACCTACACACCGTCAGCGACTGTGACACCAGCTCCATCTGT
GAGGATTCCTTTGATGGCAGGAGCCTGTCCAAGCTGAACCTGTGTGAGGATGGTCCATGTCAC
AAACGGCGGGCAAGCATCTGCTGTACCCAGCTGGGGTCCCTGTCGGCCCTGAAGCATGCTGTC
CTGGGGCTCTACCTGCTGGTCTTCCTGATTCTTGTGGGCATCTTCATCTTAGCAGTGTCCAGG
CCGCGCAGCTCCCCTGACGACCTGAAGGCCCTGACTCGCAATGTGAACCGGCTGAATGAGAGC
TTCCGGGACTTGCAGCTGCGGCTGCTGCAGGCTCCGCTGCAAGCGGACCTGACGGAGCAGGTG
TGGAAGGTGCAGGACGC

FIGURE 399

ATCCTGGACTTGACCCAGGNGTCCGTTGATTGGAACCGGTGGTCGGCAAAACAAGTCCGCTGG
GCAGCAGGAGNAGCAGNAGGATTATTAAATAACGCAGTTGGACTCTGGCAACTGGGAGTGAAG
AGGAGCCCAACAGCCGAGAAGGGAAGGAGGCANAGGAGGGGGACCAGAAGGACACCCCCGTGC
CCCGAAGACATAAATCCCTGAGTGCCCGGGAGGAGCCTTAACAAGCGCACGGAGCCCTCAAGG
TGCAAAGTTGGCTTTCACAGTGCAAGCCTTTGATTCCCAATGGGGGACTCAGGATCAAGACGA
TCTACCCTGGTCTCCCGGTTGCCAATATTCAGAAGAAGTATTAACAGAAGACATGATTCTCTT
CCTTCTTCACCTTCTTCCAGTAATACAGTTGGTGTCCACAGTTCCTCTCCTTCCAGCACTAAC
TCAAGCTCAGGTAGCACAGGTAAACGGAGGAGCATATTCCGTACTCCTTCCATTAGCTTCCAC
CATAAGAAGGGGAGTGAGCCTAAGCAAGAGCCTACCAACCAG

FIGURE 400

GGCTTCCCTCGCGCCCCACCGNCCTNTTCCGGAAGGCGGCTCCCTCCCTGCGCAGCCCGGAGC
CCCTGAGATCAGCCTCGAGCAGGCGCCCGAGCGAGACTATCCCTAAACGGGAACGGCGGTGGC
CGACTCGCGAGTGAGGAAAAGAAGGAAAGGGCAGACTGGTCGCGAAGAGAAGATCCAGGCCTC
AGAGGAGGAGAAAGGCCGGAGCCAGCCGAGCTGTCACGACCGGAGGGGGGACTCGCAGCCTTA
CCAGGGGGGTGATGTTTTACAGGCACTTAAGTATTCATCGAAGAGTCACCCCAGTAGCGGTGA
TCACAGACATGAAAAGATGCGAGACGCCGGAGATCCTTCACCACCAAATAAAATGTTGCGGAG
ATCTGATAGTCCTGAAAACAAATACAGTGACAGCACAGGTCACAGTAAGGCCAAAAATGTGCA
TACTCACAGAGTTAGAGAGAGGGATGGTGGGACCAGTTACTCTCCACAAGAAAATTCACACAA
CCACAGTGCTCTTCATAGTTCAAATTCACATTCTTCTAATCCAAGCAATAACCCAAGC

FIGURE 401

TAACAACCACAGAAACTGGANTAGTGGTCCTACAGTAGCTGCAGCTGATACCACTGAAACTAA
TTTCCCTGAAACTGCTAGCACCACAGCAAATACACNTTCTTTCCCAACAGNTACTTCACCTGC
TCCCCCCATAATTAGACACATAGTTCCTCCACAATTCCTACACCTGCTCCCCCCATAATTAGT
ACACATAGTTCCTCCACAATTCCTATACCTACTGCTGCAGACAGTGAGTCAACCACAAATGTA
AATTCATTAGCTACCTCTGACATAATCACCGCTTCATCTCCAAATGATGGATTAATCACAATG
GTTCCTTCTGAAACACAAAGTAACAATGAAATGTCCCCCACCACAGAAGACAATCAATCATCA
GGGCCTCCCACTGGCACCGCTTTATTGGAGACCAGCACCCTAAACAGCACAGGTCCCAGCAAT
CCTTGCCAAGATGATCCCTGTGCAGATAATTCGTTATGTGTTAAGCTGCATAATACAAGTTTT
TGCCTGTGTTTAGAAGGGTATTACTACAACTC

FIGURE 402

CCACAGTATGGAAGAATATCCCTGACTTCTAGCCCTGTGCGCCTTCTTTTGTTTCTGCTGTTG
CTACTAATAGCCTTGGAGATCATGGTTGGTGGTCACTCTCTTTGCTTCAACTTCACTATAAAA
TCATTGTCCAGACCTGGACAGCCCTGGTGTGAAGCGCAGGTCTTCTTGAATAAAAATCTTTTC
CTTCAGTACAACAGTGACAACAACATGGTCAAACCTCTGGGCCTCCTGGGGAAGAAGGTAAAT
GCCACCAGCACTTGGGGAGAATTGACCCAAACGCTGGGAGAAGTGGGGCGAGACCTCAGGATG
CTCCTTTGTGACATCAAACCCCAGATAAAGACCAGTGATCCTTCCACTCTGCAAGTCGAGATG
TTTTGTCAACGTGAAGCAGAACGGTGCACTGGTGCATCCTGGCAGTTCGCCACCAATGGAGAG
AAATCCCTCCTCTTTGACGCAATGAACAT

FIGURE 403

GTCGGGTGGTACGGCCGCTCCCTGCAGGNGAGTTCGTGNACGACGACGTGTGGGCGATCGTGA
ACAAACCCCGACGTGCGGGCCCGGCGCCCCGCTCCGTTGGGGCATCTTCACCAACGACTTNTG
GGGCAAGGGCATGGCCGAGAACACCAGCCACAAGTCCTACCGCCGCTTTGCGTCCTCACCTTC
AAGCTAAACATATTTTTGACTGGTATGAACCCATTCTACTTTCATGCAGTAAATATAATTTTA
CACTGCTTAGTGACTCTTGTGCTGATGTACACCTGTGATAAAACTGTCTTCAAGAATCGTGGA
CTTGCTTTTGTAACGGCATTGCTTTTTGCTGTACATCCTATTCATACTGAGGCGGTGGCTGGG
ATCGTTGGCAGAGCGGACGTGTTAGCGTGTCTGCTGTTTCTATTGGCCTTTCTCTCGTACAAC
AGGAGTCTGGATCAGGGCTGTGTTGGGGGAAGTTTCCCTTCCACGGTGTCTCCCTTCTTCTTG
CTGCT

FIGURE 404

CTTGTTTGGTCGGTGGAATATGTTGGGATTTATGTTTGCCTCTGAACAAGTGTCTTGCTCACA
TCGTAAATGACTTTCTCTCCGAAACGCTAAATATTCTTTCCCGCAGGAGCTCATATCCTTATT
TTCCATGACAGATCTTAACGGACAATATATGCAAAAGATATATAAAGATGATAACTAATATAG
TTATACTGAGCCTGATCATTTGCATTTCGTTAGCTTTCTGGATTATATCAATGACTGCAAGCA
CCTATTATGGTAACTTACGACCTATTTCTCCGTGGCGTTGGCTGTTTTCTGTTGTTGTTCCTG
TTCTGATCGTCTCTAATGGCCTTAAAAAGAAAAGTCTAGATCACAGTGGGGCTCTAGGAGGGC
TAGTCGTTGGATTTATCCTAAC

FIGURE 405

AATGCCCCCAAGTTAAATACCTCCTCNACCTTTACNTAAGTTGCTCCTTTATTTTTATTTTAT
TATTATTATTATTATTATTATTTTTTGAGATGGAGTCTCACTTTGTAACCCAGGNTGGAATGC
AATGGCATGATNTCAGCTCACTGCAACCTCCGCCTCNTGGGTTCAAGCAAGTNTCCTGCCTCA
GCCTCCGAGTAGCTGGGACTACAGGTGCACGCCACCACGCCTGGCTAATTTTTTGTATTTTAG
TAGAGACGGGGTTTCACCGTGTTGCCCAGGCTGGTCGCGAACTCCTGAGCTCAGGCAATCCGC
CCACCTCAGCCTCCCAAAGTGTTGGGATTACAGGCATGAGCCACCATGCCCAGCT

FIGURE 406

GGGCTTGAAAATCTAAATACTTTGAAATTAGAATAATATCTTGTGTTTTAGAGCTTTAAATTT
TCAAATATNTGCTGTCCACACACCCCATTGGAGGAGGACCTGTGTCACTAACCCAAATTTGTA
GCTGAGAAAACAGAGGCAGAGAGAGGTTAAGTAAAAAACCCCAAGAGAGTTCACCTAATATTG
TGAAGAAAGCAAACCCAGGGTTTCACTAACTTGTCCATGTGTGTATGTGTGTGGCTGCGTTCA
CCCCTGTGTGTGTGTGTACTGTGTGCATGCCTGTGTGTTTGTGCACACCCATGTGTATGTACC
TGCATACACACCCAAGTGTGTGTGTTACCACAACGAAAGCGCAGATTTATTGAAAAGAAAGTG
CACTCCACAGAGTGGGAGCAGGCTAGAGCCAGTGGCTCAGGAGCCTGGTTACAGCATTTTCTG
GAGTTTAAGTGCCCTCCAGAGTTTTCCCATTG

FIGURE 407

CAGCCAGGCCAGAGAGGGAGCCGAGCCAGGCCATNTCCAACCATGTCCGANGAGGCCTCGGCC
ATCACTTCCTACGAGAAGTTTCTTAACCCCCGAGNAGCCCTTCCCACTCCTGGGACCTTCCTC
GCGGGGGGGCACCTGCCCGAGCAAGGAGCCGGGCTGCCTGGACATCAAGCGACTTCGGGTGCC
AGCTGTCCTCCTGCCATCGCACCGACCCGCTCCACCGCTTCCACACCAACAGGTGGAACCTAA
CTTCTTGTGGAACAAGTGTTGCCAGCTCAGAAGGCAGTGAGGAGCTGTTTTCATCTGTGTCTG
TTGGAGATCAAGATGATTGCTATTCCCTGTTAGATGATCAGGACTTCACTTCTTTTGATTTAT
TTCCTGAGGGGAGTGTCTGCAGTGATGTCTCTTCTTCTATTAGCACTTACTGGGATTGGTCAG
ATAGCGAGTTTGAATGGCAGTTACCAGGCAGTGACATTGCCAGTGGGAGTGATGTACTTTCTG
ATGTCATACCCAGTATTCCAAGTTCACCTTGCCTG

FIGURE 408

TCAAAAAGGTTGCATTCNTTTTGCATAAACAGGGACTTTATATAGTTAACTCCCNTTATATAA
ATTCTCCTATAGTAATCTCAAAGAGTATTNTAGACTTCTCAATGCTTTTTATTGTTGCTGAAA
AGCAAAAAGACTTGCTGTGNAAGTGGAGAAGACTTCAACATCAAAGTGATTTTTTCTACTCTC
CTAGGAATGAAAGGAACACAAAGGGACCCGGAAGCATTTCTTGTCCAGATTGTGTCAAAATCT
CAATTGCCATCTGAGAATAGAGAAGGTAAAGTGCTGTGGACTGGCTGGTTCTGCTGTGTATTT
GGAGACAGTCTTCTGGAGACTGTTTCAGAAGATTTCACCTGTCTGCCCTTATTCCTTGCAAAT
GGAGCAGAGTCTAACACAGCAATAATTGGAACTTGGTTTCAGAAAACCTTTGACTGTTATTTC
AGTCCTTTAGCAATCAATGCATTTAATCTTTCCTGGATGGCTGCCATGTGGACTGCATGCAAA
ATGGACCATTATGTGGCTACTACTGAATTTCTTTGGTCTGT

FIGURE 409

GACATTTATTTTTCATCCATTGCAACCCATTGCCATAAGAACATNCCCATGGCCTTGAAGCGC
TTCACAGCAGCATNGTGGAATGCAGAATTGGAGCCAAGCAATTTTCAAAGCAAGNTTNCTGAA
AATGAAAAAAAAATACTTATATTGAAAAACTTTTTGAGCGTTATGGTGAAAATGGAAGATTATC
CTTTTTTGGTTTGNAGAAACTTTTAACAAACTTGGGCCTTGGAGAGAGAAAAGTAGTTGAGAT
TAATCATGAGGATCTTGGCCACGATCATGTTTCTCATTTAGATATTTTGGCAGTTCAAGAGGG
AAAGCATTTTCACTCACATAACCACCAGCATTCCCATAATCATTTAAATTCAGAAAATCAAAC
TGTGACCAGTGTATCCACAAAAAGAAACCATAAATGTGATCCAGAGAAAGAGACAGTTGAAGT
GTCTGTAAAATCTGATGATAAACATATGCATGACCATAATCACCGCCTACGTCATCACCATCG
TTTGCATCATCATCTTGATCATAACAACACTCACCATTTTCATAATGATTCCATTACTCCCAG
TGAGCGTGGAGCGGCCGC

FIGURE 410

TACCTATTCCCAGGTTTAATGTTGATTATTTATATTTGAAAAAANTTGATTTGTANAAACTGG
GTANATTACTTTCAAATTAATCATTTATTCCTAATTGACCAGGGATGAGTGAGATGTTTATTT
AGAAAACAAATAATTTTAGATAGGAAAATTGAATCTTTAAAAAATAATGGTGATTTAATATAT
CAATGTGTGGTTTTTGTGTGTATGTGTGTAANATTGGAGCATCCAGGAGTGTGCGGTGTGTAT
ATGACCTTATTTTTCTACTGTATCTTAGAGGTTGCCNCTTCCATGGGTATAAAACTTAATTGG
ATTTCTCGATTTTTATTTTGTTTATGCACTTTTACAACTTATGTCATTTTAGGTTGTTTATTA
ATGCCAGTTTTGTATAATAAAATTATTAGAGAAGTTATGAAGGAGGATGGCATGAGTGGGGCG
GCCGN

FIGURE 411

ACGCAGAGCGTTTTCATTTTCCACGGGTCTGTCCTTGTCAAAGCACACCCCTCGGTGTCCAGG
TTCNTCATGGGCAAGTGCTCGGGGTGACAAANAAGGCGACATTGACTACAGCACCGTGCTCCT
CGGCATGCTGGTGACGCAGGACGTGCAGCTCGGGCTTTTCATGGCTGTCATGCCGACTCTCAT
ACAGGCGGGCACCAGTGCATCTTCTAGCATTGTCGTGGAAGTTCTCCGAATCCTGGTTTTGAT
TGGTCAGATTCTTTTTTCACTAGCGGCGGTTTTTCTTTTATGTCTTGTTATAAAGAAGTATCT
CATTGGACCCTATTATCGGAAGCTGCACATGGAAAGCAAGGGGAACAAAGAAATCCTGATCTT
GGGAATATCTGCCTTTATCTTCTTAATGTTAACGGTCACGGAGCTGCTGGACGTCTCCATGGA
GCTGGGCTGTTTCCTGGCTGGAGCGCTCGTCTCCTCTCAGGGCCCCGTGGTCACCGAGGAGAT
CGCCACCTCCATCGAACCCCC

FIGURE 412

CAGTTTTTTTATAGTGAATACCAAAANCATCAGCAANCACTGGACTGTCAACCCAAGGCTTAT
TGATATTTGCGGAGTTGATTTCTGCGATTAAGAGACGTTGGCTCGCCTTCNTCGTGATCATTG
TGAGCCTGGGCTATGGCATTGTGAAGCCTCGTTTAGGAACAGTCATGCACCGGGTGATCGGAC
TGGGGCTTCTATACTTAATCTTTNCAGCTGTTGAAGGCGTGATGAGAGTCATTGGGGGTTCTA
ACCATTTAGCTGTTGTTCTTGATGACATTATTTTAGCAGTTATTGACTCCATTTTTGTGTGGT
TCATTTTTATTAGTTTGGCACAAACTATGAAGACCCTAAGGCTAAGAAAGAACACTGTGAAAT
TTTCATTATATAGACATTTTAAAAATACTCTGATCTTTGCTGTGCTGGCTTCTATAGTGTTTA
TGGGGTGGGCGGCCGC

FIGURE 413

ACGTGGTCTGCCTGTTATTGGAAAGATATATTAAGATCCAGTTCTGGATTNCANCTGTTTATT
TTTTTGGGAAATGCTTNAAAAAGCAGTTTTTTTATAGTGAATACCAAAACATCAGCAACACTG
GACTGTCAACCCAAGGCTTATTGATATTTGCGGAGTTGATTTCTGCGATTAAGAGGACGTTGG
CTCGCCTTCTCGTGATCATTGTGAGCCTGGGCTATGGCATTGTGAAGCCTCGTTTAGGAACAG
TCATGCACCGGGTGATCGGACTGGGGCTTCTATACTTAATCTTTGCAGCTGTTGAAGGCGTGA
TGAGAGTCATTGGGGGTTCTAACCATTTAGCTGTTGTTCTTGATGACATTATTTAGCAGTTA
TTGACTCCATTTTTGTGTGGTTCATTTTTATTAGTTTGGCACAAACTATGAAGACCCTAAGGC
TAAGAAAGAACACTGTGAAATTTTCATTATATAGACATTTTAAAAATACTCTGATCTTTGCTG
TGCTGGCTTCTATAGTGTTTATGGGGTGGGCGGCCGC

FIGURE 414

ACCGGCCCGTGAGCCGGCCNTGCGCCGGCAGGTCGCGGACATACTGTGGCGCGTTTTGGGCT
GGAGGATAGTTGCAAGTATTGTTTGGTCAGTGCTATTTCTACCCATCTGCACCACAGTATTTA
TAATTTTCAGCAGGATTGATTTGTTTCATCCTATACAGTGGCTGTNTGATTCTTTCAGTGACC
TGTATAGTTCCTATGTAATCTTTTACTTCCTGCTGCTGTCAGTGGTAATAATAATAATAAGTA
TTTTCAATGTGGAGTTCTATGCAGTTGTGCCTTCTATTCCTTGCTCCAGACTAGCTCTGATAG
GGAAGATCATTCATCCTCAGCAACTCATGCACTCATTTATTCATGCTGCAATGGGAATGGTGA
TGGCCTGGTGTGCTGCAGTGATAACCCAGGGCCAGTACAGCTTTCTTGTGGTTCCCTGCACTG
GTACTAACAGCTTTGGTAGCCCTGCTGCGCAAACCTGCTTAAATGAATATCATCTTTTTTTCC
TACTGACTGGAGCGGCCGC

FIGURE 415

GNCCACACTGGCCAAACGGGGCATCATGGNCACACTGCCNAAATAGGGCCGCCATGTTGCAGC
AGGATAGTAATGATGACCCTGAAGATGTTTCACTGTTTGATGCGGAAGAGGAGNCGACTAATA
GACCAAAAAAGCCAAAATCAGACATCCAGTAGCATCGTTTTTCCACTTTATTCTTTCGAGTCA
GTGCAATCATCGTCTATCTTCTCTGTGAGTTGCTCAGCAGCAGCTTTATTACCTGTATGGTGA
CAATTATCTTGTTGTTGTCGTGTGACTTTTGGGCAGTGAAGAATGTCACAGGTAGACTAATGG
TTGGCCTACGTTGGTGGAATCACATTGATGAAGATGGAAAGAGCCATTGGGTGTTTGAATCTA
GAAAGGAGTCCTCTCAAGAGAATAAAACTGTGTCAGAGGCTGAATCAAGAATCTTTTGGTTGG
GACTTATTGCCTGTCCAGTACTGTGGGTGATATTTGCTTTTAGTGCACTCTTCTCCTTCAGAG
TAAAGTGGTTGGCGGTGGTTATCATGGGTGTGGCGGCCGC

FIGURE 416

CAGCAGTCCTTATGATTATGGAGGAAAGTGGAGGNCCCTTATAGCNAAACAGGTATGCTGGNT
ATGACNTATTCGCAGCAAAGGCAGATTTGTCCCCTCCAGACATGATGCAGCCACAACAGCCAT
ACACCGGGCAGATTTNCCAGCCAACTCAGGCATATACTCCAGCTTCACCTCAGCCTTTNTATG
GAAACAACTTTGAGGATGAGCCACCTTTATTAGAAGAGTTAGGTATCCAATTTTGACCACATN
TGGCAAAAAACACTAACAGTATTACATCCGTTAAAAGTAGCAGATGGCAGCATCATGAATGAA
ACTGATTTGGCAGGTCCAATGGTTTTTTGCCTTGCTTTTGGAGCCACATTGCTACTGGCTGGC
AAAATCCAGTTTGGCTATGTATACGGGATCAGTGCAATTGGATGTCTAGGAATGTTTTGTTTA
TTAAACTTAATGAGTATGACAGGTGCGGCCGC

FIGURE 417

TAATTGTTTATTGGGAAATGGAGGATTAAGNACATTTTTCAATTTGTGCATGNAGAGGAAGAC
CTGAAGGTTCAGCATANTAGCTACAAGACAGANGGGCCCGGCTGTTNAAGGACCAGCTCTCCC
TGGNAAATGTGCACTTTCAGATCACAAGATGTGAAATTGCAGGATGCAGGGGTGTACCGCTGC
ATGATCAAGCTATGGTGGTGCCGACTACAAGCGAATTNCTGTGAAAGTCAATGCCCCATACAA
CAAAATCAACCAAAGAATTTTGGTTGTGGATCCAGTCACCTCTGAACATGAACTGACATGTCA
GGCTGAGGGTTACCCCAAGGCCGAAGTCATCTGGACAAGCAGTGACCATCAAGTCCTGAGTGG
TAAGACCACCACCACCAATTCCAAGGGAGAGGCGGCCGC

FIGURE 418

AGGTGCTTGTGCTCGAACCCAGTGGTTGGGGCGGTGCTCCTCAAGCTTGTGTGCCTGCTAACC
NTCNTGNGTCCGGGNTGGCAAGAGTGTGGGACTTTCCCCCTGGCGNCCGTGGACAACATGATG
GTCAGAAAAGGGGACACGGCGGGTGNTTAGGTGTTATTTGAAAGATGGAGCTTCAAAGGGTGC
CTGGCTGAACCGGTCAAGTATTATTTTTGCGGGAGGTGATAAGTGGTCAGTGGATCCTCGAGT
TTCAATTTCAACATTGAATAAAAGGGACTACAGCCTCCAGATACAGAATGTAGATGTGACAGA
TGATGGCCCATACACGTGTTCTGTTCAGACTCAACATACACCCAGAACAATGCAGGTGCATCT
AACTGTGCAAGTTCCTCCTAAGATATATGACATCTCAAATGATATGACCGTCAATGAAGGAAC
CAACGTCACTCTTACTTGTTTGGCCACTGGGAAACCAGAGCCTTCCATTTCTTGGCGACACAT
CTCCCCATCAGCAAAACCATTTGAAAATGGACAATATTTGGACATTTATGGAATTACAAGGGA
CCAGGCTGGGGCGGCCGC

FIGURE 419

TAAACTACACTCAGTATACAGTGATAGTGGGATTTGAACACCTGAAGCTCCCCATCAAAGGGA
ATGAACTTCACATGAAGACTTATAACCCTGCCTTCTCCCGGGTTGGAAATCTGGTTCCGGTTT
TTCTTTGTGGTGCTCACCTTCATCGTCACTTGCCTGTTTGCGCATTCCCTCCGGAAATTTTCC
ATGAGAGACTGGGGCATCGAGCAGAAGTGGATGTCTGTTCTCCTGCCTCTGCTGCTACTTTAC
AATGATCCGTTCTTCCCCCTCTCCTTCCTGGTCAACAGCTGGCTCCCAGGGATGCTGGATGAC
CTCTTTCAGTCCATGTTCCTGTGCGCCCTGCTGCTCTTCTGGCTGTGCGTGTACCACGGGATT
CGTGTCCAGGGAGAAAGAAAGTGTTTAACTTTCTATTTGCCTAAATTCTTCATTGTTGGACTA
TTGTGGTTGGCTTCTGTTACGCTAGGAATATGGCAAACAGTTAACGAATTACATGATCCAATG
TACCAGTATCGAGTTGATACCGGAAATTTTCAGGGAATGAAGGTCTTCTTCATGGTGGGGGCA
GCGGCCGC

FIGURE 420

GTGTCTGCTCGCCCTCCGACGCTGCTCAGGAATTTGCAAGAAACTGAAGTTTTGATTCAGATA
TATTTTGAATTGAAACCAGAGATGTTNTAGAGTTTAGATTCTTTCATTTGATTAAGGTATGGT
CTGAATATGCGTTGCTTGGCAGCTCGGGTCAACTATAAGACTTTGATTATTATCTGCGCACTC
TTCACTTTGGTCACAGTACTTTTGTGGAATAAGTGTTCCAGTGACAAAGCAATCCAGTTTCCA
CGGCGTTCGAGTAGTGGCTTCAGAGTGGATGGGTTTGAAAAAAGAGCAGCAGCATCTGAGAGT
AACAACTATATGAACCACGTGGCCAAACAACAGTCTGAGGAAGCATTCCCTCAGGAACAGCAG
AAAGCACCCCCTGTTGTTGGGGGCTTCAATAGCAATGTGGGAAGTAAGGTGTTAGGGCTCAAA
TATGAAGAAATTGACTGTCTCATAAATGATGAACACACAATTAAAGGGAGACGAGAGGGGAAC
GAAGTCTTTCTTCCATTCACTTGGGTTGAGAAATATTTTGATGTTTATGGAAAGGTGGTGGCG
GCCGC

FIGURE 421

AGGCTCCCGTGTCTGCTCGCCCTCCGACGCTGCTCAGGAATTTGACAAGAAACTGAAGTTTTG
ATTCAGATATATTTTGAATTGAAACCAGAGATGTTCTAGAGTTTAGATTCTTTCATTTGATTA
AGGTATGGTCTGAATATGCGTTGCTTGGCAGCTCGGGTCAACTATAAGGCTTTGATTATTATC
TGCGCACTCTTCACTTTGGTCACAGTACTTTTGTGGAATAAGTGTTCCAGTGACAAAGCAATC
CAGTTTCCACGGCGTTCGAGTAGTGGCTTCAGAGTGGATGGGTTTGAAAAAAGAGCAGCAGCA
TCTGAGAGTAACAACTATATGAACCACGTGGCCAAACAACAGTCTGAGGAAGCATTCCCTCAG
GAACAGCAGAAAGCACCCCCTGTTGTTGGGGGCTTCAATAGCAATGTGGGAAGTAAGGTGTTA
GGGCTCAAATATGAAGAAATTGACTGTCTCATAAATGATGAACACACAATTAAAGGGAGACGA
GAGGGGAACGAAGTCTTTCTTCCATTCACTTGGGTTGAGAAATATTTTGATGTTTATGGAAAG
GTGGGGGCGGCCGC

FIGURE 422

TTCTTTTTTTTCCCCCNGCAATTTTTTCAGTGAAANACATGGAGTCTTTCATCTTGGAGAGTT
GTCAGAGTCAAGATTTTGCTGTTGTAGCCAGTGCTTTAAAACAATTCACAAAGACTTTCTAGG
AGAGGAAGAGAGNCTGAGGGAAGAAGAGATACAGAAAAAGAAAATGNCAGGATTGAACCTGGA
AACTCACAGAATCTCTGACTCATGCTGGAAATGTNTTTGGGTACCTCTTGCCTTTTNTGTGTT
GGCGGCGGCCGC

FIGURE 423

TGAAAGGACCCCTAGTTCCCCTGGCAAATGNTTTTNTTCAATCCCCCACTTCATTTTCCTTAA
GAGCCATTCCAAGTNTCTTCCTTTNTCGATACCCCAACCAGCTCACATCCCACTCAAGGGGTG
AGATGCCCTCCTCACCATTGAAGAGATCAAGCCCCCAGGGGGGAACCAGCTCAACTTCCCCCT
CTGTCTCTCCGAAGAGCNTCCTGTTTGAAAACTCGAGGCAGCTGTACCCCGTGCGAAGTTCTT
GCTCCCGTCTCCCCATGTCTTCCAGGATTTTCCTTCATAGTGGGGATTACTCGCTAACCTTTC
CTTCCTCACCTACTTCCCCTTTTCCTTCAGCTTTCACCGTGTTTAAATCTTCTAATAATTCTT
TTTATGACATCTTGTTTTTCAAGCTCTTCTCCAGTGATCCCTCCACTTCTCCAATGGCCCTTT
TCACTAAACCTCCAAATTTGTCTTTGCTGACATTTATTGAGCTGCTATTACATGTTCTAAATG
CTTTACTTGTCGTATTTAATCCTAACAACAACCTACAAGGTAGGCCTTGCTATTATCTCCATT
TTATAGTTGAAGAAACTGAGGCTGCCGCGGCCGC

FIGURE 424

TATCGGCACATTGGCAAAGACAACATTCAGGCCCAATGGCCCACAAATTGGTCCGCCCAATGC
CATTNTGNAAAAGGNTTCACTGCAAATTACAAAAGCATCCNTNATGAAAAGAGATTGGAAAGG
CCTCTCCAAGCAACTGGACTGGGATGTTCGAAGCATTCAGCGCTGGTTCGCAAAGACGCAATC
AGGANAAGCCCAAGCACGGCTGACGAGGTTCTGTGAGAGCATGTGGANATTTTCATTTTACCT
TTATGTATTTACCTACGGAGTCAGATTCCTGAAAAAGACCCCCTGGTTGTGGAATANGAGGCA
TTGNTGGTACAACTACCCCTATCAGCCACTCACAACTGACCTTCACTACTATTACATCCTGGA
GCTGTCGTTTTATTGGTCTTTGATGTTTTCTCAGTTCNCTGATATCAAAAGAAAGGACTTTGG
CATTATGTTCCTGCACTACCNTGTATCTATTTTCTTGATTACCTTTTCATATGTCAACAATAT
GGCCCGAGTAGGAACGCTGGTCCTTTGTCTTCATGATTCAGCTGATGCTCTTCTGGAGGCTGC
GGCCGC

FIGURE 425

ATTTTTTGAAATTAATGCNTGAGCTTTATTTTGTTTAATTGTTATGCCCACTGGATTGGGACA
AGCATCACCTCTGAATTTTGAAGACCTTAATGTGTGTTAGCCATTGNAAAGCTACTCAAGTGC
TGTGCAAGAGTCATACCCACATCCCTTTGATCAAATTTACTACACGAGCTGCACTGACATTCT
AAACTGGTTTAAATGCACGCGGCACAGAGTCAGCTATCGGACAGCCTATCGACATGGGGAGAA
GACTATGACAGGCGCAAGTCTCAGTGTTGTCCTGGATTTTATGAAAGCGGGGAAATGTGTGTC
CCCCACTGTGCTGATAAATGTGTCCATGGTCGCTGTATTGCTCCAAACACCTGTCAGTGTGAG
CCTGGCTGGGGAGGGACCAACTGCTCCAGTGCCTGCGATGGTGATCACTGGGGTCCCCACTGC
ACCAGCCGGTGCCAGTGCAAAAATGGGGCTCTGTGCAACCCCATCACCGGGGCTTGCCACTGT
GCTGCGGGCTTCCGGGGCTGGCGCTGCGAGGACCGCTGTGAGCAGGGCACCTATGGTAACGAC
TGTCATCAGAGATGCCAATGCCAGAATGGAGCCACCTGCGACCACATCACGGGGCTGGCGGCCGC

FIGURE 426

TTTTCAATGAAAAAAAGAATCCCAAAAAAAAAAGTTGTCAGCCTCATTTGTGCGTCATCCCTT
ATTTTCCTGGGATCTCAGGACCTCTGTCCCTCTCATTTCTCACTTCTGAGATCTGCACATCTT
TTACCCAGGAGCCTCAGAGCTCCTGAGTCTGGTGTCTGCCTATCCCCATCTTCACTGTTAGTC
CTCCTGCAGATTCTGTGTCTCCTTTCATGTAGGTGCTGGATCCCTGTGTGTGGAGCGGCCGC

FIGURE 427

ACAAAGTTTCCCAATGACTTGTTAAAAGTCGATGGTGTAGCTCAAGATGGAACCCNCAATGTA
CATTAATAACAAAAGTTCACAACGGGCAAAGGACCNTCACATGTGCAAGGAAAATGTGCGGAG
ATTATTGGGCTCACCTTGGGTACNTGAACTACACTCAGTATACAGTGATAGTGGGATTTGAAC
ACCTGAAGCTCCCCATCAAGGGAATGAACTTCACATGGAAGACTTATAACCCTGCCTTCTCCC
GGTTGGAAATCTGGTTCCGGTTTTTCTTTGTGGTGCTCACCTTCATCGTCACTTGCCTGTTTG
CGCATTCCCTCCGGAAATTTTCCATGAGAGACTGGGGCATCGAGCAGAAGTGGATGTCTGTTC
TCCTGCCTCTGCTGCTACTTTACAATGATCCGTTCTTCCCCCTCTCCTTCCTGGTCAACAGCT
GGCTCCCAGGGATGCTGGATGACCTCTTTCAGTCCATGTTCCTGTGCGCCCTGCTGCTCTTCT
GGCTGTGCGTGTACCACGGGATTCGTGTCCAGGGAGAAAGAAAGTGTTTAACTTTCTATTTGC
CTAAATTCTTCATTGTTGGACTATTGTGGTTGGCGGCCGC

FIGURE 428

GCATCCGCTTGACTGCATNTGAGTTTTCCCAGTCTGTCTTTGGGGATGGGGCCATGCCATAGT
CTTGATGTCTTGTGCCGTGTGATTTTTGCAGATAAGATGACTTGGCCCATGGCCCNCAGATCA
CTTATTCTGGGGAAGTGTAGGAACAGTGGTTGCCTAACCCAAGTTCTTACATGATGTACCTTT
TTCCTTTCTAAAAAATAACTTAAAAATATGAAATATACTAATTTGTTTCAGATATTACATACA
ATTGGAAAGTGGACAAGTTCCTGTATATGCTGTCACTTTTCAAGAACCTGAGAATGATCCTCG
GAATTGCTGTTACTTGTGGGCTGTTCAGTCTACACAAGATAGGTAGGTCTCATACAAACTTTG
TTTTGTTTTGTTTTGTTTTTTTGGAGACAGAGTCTCGCTCTGTTGTCCAGGCTGGAGTGCAGT
GGCGTGATTTCGGCTCACTGCAACCTCCGCCTCCCGGATTCATGCCATTCTCTCGCTCAGCCT
CCCGAGTAGCTGGGACTACAGGTGCCTGCCACCATGCCTGGCTAATTTTTATATTTTCAGTAG
AGACGGGAGCGGCCGC

FIGURE 429

TTAATTTAAAAATATGAAAAGTAAAAATGGGATTTTGTCTTATTTGTGTTNNANAGCTGGCTT
TTCACACATGCAGTTGTTAGTGTTTACTGCCCTTGCCATTTTAATTATGAGGCTAAAGATGTT
TTTGACACCGCACATGTGTGTTATGGCTTCCTTGATATGCTCTCGACAGCTCTTTGGCTGGCT
TTTTCGCAGAGTTCGTTTTGAGAAGGTTATCTTTGGCATTTTAACAGTGATGTCAATACAAGG
TTATGCAAACCTCCGTAATCAATGGAGCATAATAGGAGAATTTAATAATTTGCCTCAGGAAGA
ACTTTTACAGTGGATCAAATACAGTACCACATCAGATGCTGTCTTTGCAGGTGCCATGCCTAC
AATGGCAAGCATCAAGCTGTCTACACTTCATCCCATTGTGAATCATCCACATTACGAAGATGC
AGACTTGAGGGCTGCGGCCGC

FIGURE 430

GGCCCNCACTGGCCAAAATAGTTGGAATGCCTTTTNTTATTCACCAATGGGGCCCAAGGGGAA
NAGTGGGTGTTTGGGGGGCCTTTTTGCACCATCATCACATCCCTGGATACTTGTAACCAATTT
GCCTGTAGTGCCATCATGACTGTAATGAGTGTGGACAGGTACTTTGCCCTCGTCCAACCATTT
CGACTGACACGTGGAGAACAAGGACAAGACCATCCGGATCAATTTGGGCCTTTGGGCAGCTTC
CTTTATCCTGGCATTGCCTGTCTGGGTCTACTCGAAGGTCATCAAATTTAAAGACGGTGTTGA
GAGTTGTGCTTTTGATTTGACATCCCCTGACGATGTACTCTGGTATACACTTTATTTGACGAT
AACAACTTTTTTTTTCCCTCTACCCTTGATTTTGGTGTGCTATATTTTAATTTTATGCTATAC
TTGGGAGATGTATCAACAGAATAAGGATGCCAGATGCTGCAATCCCAGTGTACCAAAACAGAG
AGTGATGAAGTTGACAAAGATGGTGCTGGTGCTGGCGGCCGC

FIGURE 431

AGGTGTCACCATGGCAAAGCTTCCCTTCTTGATTCTCTCGAGTTTGTTGAAGCGTNTACGGTT
NCACTGACGGATTCAGAAGCTCATTTTACCTCAGCTTTCATTGAAACTACCTCCTATCTTGAG
TCTTCACTCATTTCCCATGAATCCGCAGTCACTGCACTGGTGCCCCCCGGTCTGAGTCTTTTG
ACATTTTGACTGCCGGGATTCAAGCAACATCACCATTGACCACTGTCCACACAACGCCCATTT
TAACTGAGTCTTCTTTGTTCTCAACTCTGACACCTCCTGACGACCAAATCAGTGCTCTAGACG
GTCACGTGTCTGTCCTGGCCTCTTTCTCCAAAGCCATTCCCACTGAGCTGACCGTCGTGGGCC
CATCACTCACACCCACAGAGGTGCCACTGAACACCTCCACGGAAGTGAGCACAACCAGCACCG
GTGCTGCCACTGGTGGTCCCCTCGACTCCACCCTGATGGGTGACGCCGCAAGTCAGAGCCCCC
CAGAGAGTAGTGCTGCTCCTCC

FIGURE 432

ACACTCAGAACAGGAGNAATTTGGACTAATTTTCAAACTACAGACACTTTCTAATCATGATGC
ATTTCAAAAGTGGACTCGGAATTTAACTGNGTTGCAAAACATGNCAGTGCCCGAGGATGATAA
CATTAGCAATGACTCCAATGATTTCACCGAAGTAGAAAATGGTCAGATAAATAGCAAGTTTAT
TTCTGATCGTGAAAGTAGAAGAAGTCTCACAAACAGCCATTTGGAAAAAAAGAAGTGTGATGA
GTATATTCCAGGTACAACCTCCTTAGGCATGTCTGTTTTTAACCTAAGCAACGCCATTATGGG
CAGTGGGATTTTGGGACTCGCCTTTGCCCTGGCAAACACTGGAATCCTACTTTTTCTGGTACT
TTTGACTTCAGTGACATTGCTGTCTATATATTCAATAAACCTCCTATTGATCTGTTCAAAAGA
AACAGGCTGCATGGTGTATGAAAAGCTGGGGGAACAAGTCTTTGGCACCACAGGGAAGTTCGT
AATCTTTGGAGCCACCTCTCT

FIGURE 433

CCAACCCAATTACCAAGCAGATNCTTTTGGGGGATTCCAGCCATCAGACAAGGAACCCATGGC
AGCTGCAGGGTTTTTTGCATTGTGCAAGCTTATGCTTTCTTGCAGATNTGAGAGCCGATTAAC
AAANCAAGAGTTCCAGACCNTTTTCTTTTTGGGTGTATCACTAGCTGCAGGTGCTGTGTTCCT
TAGTGTCATCTATTTGACTTATACAGGTTACATTGCACCATGGAGTGGCAGGTTTTATTCATT
GTGGGATACTGGGTATGCAAAAATACACATTCCAATTATTGCATCAGTGTCTGAGCATCAACC
TACGACTTGGGTGTCTTTCTTCTTTGATCTACATATTCTTGTATGTACCTTCCCAGCAGGCCT
TTGGTTCTGCATCAAAAATATCAACGATGAAAGAGTATTTGTTGCTCTATATGCAATCAGTGC
TGTCTACTTTGCTGGAGTGATGGTGCGACTGATGTTGACTTTGACTCCAGTCGTGTGTATGCT
GTCTGCAATTGCCTTTTCAAATGTTTTTGAGCACTATTTGGGGGCTGCGGCCGC

FIGURE 434

ATTGCAGCTGTTATTTTTTTGGAAATGCTTGAAAAAGCAGTTTTTTATAGTGAATACCAAAAC
ATCAGCAACANTGGACTGTCAACCCAAGGCTTATTGATATTTGCGGAGTTGATTTCTGCGATT
AAGAGGACGTTGGCTCGCCTTCTCGTGATCATTGTGAGCCTGGGCTATGGCATTGTGAAGCCT
CGTTTAGGAACAGTCATGCCCGGGTGATCGGACTGGGGCTTCTATACTTAATCTTTGCAGCTG
TTGAAGGCGTGATGAGAGTCATTGGGGGTTCTAACCATTTAGCTGTTGTTCTTGATGACATTA
TTTTAGCAGTTATTGACTCCATTTTTGTGTGGTTCATTTTTATTAGTTTGGCACAAACTATGA
AGACCCTAAGGCTAAGAAAGAACACTGTGAAATTTTCATTATATAGACATTTTAAAAATACTC
TGATCTTTGCTGTGCTGGCTTCTATAGTGTTTATGGGGCGAGCGGCCGC

FIGURE 435

GGCCACACTGGCCAAACTAAAATTTTTGGTATTGCAGATGACGCTCATATTGGCAACTTACTA
ACATCAAAATTCTTTAGTTATAAGGATTTTGATACTTTATTGTATACCTGTGCAGCGGAGTTT
GACTTTATGGAAAAAGAGACTCCACTGAGATACACAAAGACATTATTGCTTCCAGTTGTTCTT
GTAGTGTTTGTTGCTATTGTTAGAAAGATTATTAGTGATATGTGGGGTGTCTTAGCTAAACAA
CAGACACATGTAAGAAAACACCAGTTTGATCATGGAGAGCTGGTTTACCATGCATTGCAATTG
TTAGCATATACAGCCCTTGGTATTTTAATTATGAGACTAAAACTCTTCTTGACACCACACATG
TGTGTTATGGCATCACTGATCTGCTCAAGACAGCTATTTGGATGGCTCTTTTGCAAAGTACAT
CCTGGTGCTATTGTGTTTGCTATATTAGCAGCAATGTCAATACAAGGTTCAGCAAATCTGCAA
ACCCAGTGGAATATTGTAGGGGAGGCGGCCGC

FIGURE 436

AGGGTTTTAATAGGACTANCAGTACGATGGGCAGTGTCTNTTAATTTTTATTCAGGNGCTGGT
AANCCGCCTATGTTTGGTGATTATGAAGCTCAGAGACCTGGCAAGAAATAACTTTTTAATTTA
CCGGTCAAACAATGGTATTTTACCAGCAGTGATAACAATTTACAGTATTGGGGATTGGATTAC
CCACCTCTTACAGCTTATCATAGTCTCCTATGTGCATATGTGGCAAAGTTTATAAATCCAGAC
TGGATTGCTCTCCATACATCACGGTGGATATGAGAGTCAGGCACATAAGCTCTTCATGCGTAC
AACAGTTTTAATTGCTGATCTGCTGATTTACATACCTGCAGTGGTTTTGTACTGTTGTTGCTT
AAAAGAAATCTCAACTAAGAAAAAGATTGCTAATGCATTATGCATCTTACTGTATCCAGGCCT
TATTCTTATAGACTATGGACATTTTCAATATAATTCTGTGAGTCTTGGCTTTGCTTTGTGGGG
TGCGGCCGC

FIGURE 437

CACTGGCCAAAAAATTCGATGCGAGGCCCAGNAAGCACGCTGAAACCNTGGCGGCGGCAAGCT
GTGCGACTNTTTTGCGGCCGGCCTGGGCAGGTGTCTTCCTCGAGAGGCAGGCAGGGGATCCCG
GACACTAGCTTTATCGTCATCTGGGAAATTGTTAAAAATGCAAATTCGCAAGTTTGAGAGCCA
TGGTTCCAAGAAACTGCATAAGCATACGAAATAAGTTGCAGCCTCCCGACTTATACCCTGGTA
CTTCTAGTCTAAAACAGGATTTGACTCTACTAATCCAGCCTTATACAGGATGCTGTGTTCTTT
GCTCCTTTGTGAATGTCTGTTGCTGGTAGCTGGTTATGCTCATGATGATGACTGGATTGACCC
CACAGACATGCTTAACTATGATGCTGCTTCAGGAACAATGAGAAAATCTCAGGCAAAATATGG
TATTTCAGGGGAAAAGGATGTCAGTCCTGACTTGTCATGTGCTGATGAAATATCAGAATGTTA
TCACAAACTTGATTCTTTAACTTATAAGATTGATGAGTGTGAAAAGAAAAAGAGGGGTGCGGC
CGC

FIGURE 438

AGAAAAAGAAGAATCAACGTAAATAAGATAAANGGATTCAAAATAAAGATNTCTTGAAGAGAA
ATAAGAATCATTTACAAAAGCAGCAGAGAAAAATTTTACAGATGAAGGAGCCAGCTATTTAAG
ATGGGCATCAAGGTTCTCCAGCAGTCTAAAAGCCAAAAACAAAAAGAAGAAGCCTACCTACTT
TTTGCCAAAGCAGCTGACATGGGAAACTTGAAAGCTATGGAGAAAATGGCTGACGCTTTGCTA
TTTGGAAATTTTGGCGTGCAAAATATAACAGCAGCTATCCAATTATATGAGTCCTTGGCTAAA
GAAGGATCATGTAAAGCCCAAAACGCATTAGGATTTTTGTCTTCTTATGGAATAGGAATGGAA
TATGATCAAGCTAAGGCACTGATATATTACACCTTTGGAAGTGCTGGAGGAAACATGATGTCC
CAGATGATTTTGGGGTACAGATATTTGTCGGGAATCAATGTTCTACAGAATTGTGAAGTTGCC
CTAAGTTATTACAAGAAAGTGGCAGATTATATTGCTGACACATTTGAAAAAAG

FIGURE 439

TTTTGTTGCCTTGGGTGTTCTCACACTCTGCAAGTTTTACTTGCAGGGTTATCGAGTTTTCAT
GAATGATCCTGCCATGAATCGGGGCATGACAGAAGGAGTAACGCTGTTAATCNNTGGCAGTGC
AGACTGGGNTGATAGAACATGCAGGTTGTTCATCGGGCATTCTTGCTCAGTATTATCCTTTTC
ATTGTCNGTAGCTTCTATCCTACAGTCTATGTTAGAAATTGCAGATCCTATTGTTTTGGCACT
GGGAGCATNTAGAGACAAGAGCTTGTGGAAACACTTCCGTGCTGTAAGCCTTTGTTTATTTTT
ATTGGTATTCCCTGC

FIGURE 440

ACCACCTTGCCCATTTATTTTGGCCCTTGTTAAACCAATAACTGCNTATCCAGATATGCCACA
NTTTTGCCTGCTGTGGCANCCNTCNTGGATAGGTGCTCTTGTTAATCACATGGATGTTATATA
AGAGTTGGGCCGGCCCAGCACACAAGGTCAGCATGTGCTCTTNTGTCACGCTCTCGCTATAGC
TGTTGTCCAGATCGTTATCTTCTCAGAAAGCTGGGCATTTGCCAAGAACATCAACTTCTATAA
TGTGAGGCCTCCTCTCGACCCTACACCATTTCCAAATAGCTTCAAGTGCTTTACTTGTGAAAA
CGCAGGGGATAATTATAACTGCAATCGATGGGCAGAAGACAAATGGTGTCCACAAAATACACA
GTACTGTTTGACAGTTCATCACTTCACCAGCCACGGAAGAAGCACATCCATCACCAAAAAGTG
TGCCTCCAGAAGTGAATGTCATTTTGTCGGTTGCCACCACAGCCGAGATTCTGAACATACGGA
GTGTAGGTCTTGCTGTGAAGGAATGATCTGCAATGTAGAATTACC

FIGURE 441

ATTTATTTTGCTAAATTGAAAGGGAACATAGATGGAATTCCAAAATATGTACATTCAGCTGTT
TGGTTTTTCGTTTTTCATTGTTATTATTGTGAGAATGCTGTTATTGGGGTTGTGTGTGAGTGC
CCGTCAGCCAGTGATGCCTCGGGCCACGCTGTGGGGCCACCTCAGTCCTGCCTGGGTCCTGGT
GCCTTGGACCCCACGTGCTTGTGGCCAGGCTGCCCCTGGGCGGGGCCATGTGGCCTCAGACCA
CAAGAGCGGAGCTGCCCTGGCCCAAGCACTGCAGCTGCCTGCACCCCCGGG

FIGURE 442

CGACCGCCCTTCGCGGGGCAGNAAGGCCAGGGGTGCTNAGTTCTTTCACCTCCTTTTAGACTN
AAGATTTGCCAAGTTTTCCGGCATTGNTCTTGAGGATCTCAGAAGGGCTCTTTAAGCAAGACT
GCAAATGGGTGNGTATTTGTCATGAACCGAATGAATTCCCCAGAACAGTGGTTTCACTCAGCG
CAGGGGAATGGCTCTTTGGGATTGTTATTCTTCTGCTTGTTGATGTGATATGGGTTGCTTCCT
CTGAACTTACTTCGTATGTTTTTACCCAGTACAACAAACCATTCTTCAGCACCTTTGCAAAAA
CATCTATGTTTGTTTTGTACCTTTTGGGCTTTATTATTTGGAAGCCATGGAGACAACAGTGTA
CAAGAGGACTTCGCGGAAAGCATGCTGCTTTTTTTGCAGATGCTGAAGGTTACTTTGCTGCTT
GCACAACAGATACAACTATGAATAGTTCTTTGAGTGAACCTCTGTATGTGCCTGTGAAATTCC
ATGATCTTCCAAGTGAAAAACCTGAGAGCACAAACATTGATACTGAAAAAACCCC

FIGURE 443

GACCTCGACCCAAGGGTCCGCGGANGGGTGGGACTGGTCATGGATCTTTNGTCAAGAATGAGT
TTCGGCCCCCTCCTACCTTATGGGCTATAATAAATCCTTGAGTGTGGGGCAACCACAACTTTT
CTGACTGGGATTATTCAGCTAATAATGGGCGTATTGGGTTTGGGTTCATTGCCACTTACCTTC
CGGAGTCTGCAATGAGTGCTTACCTGGCTGCTGTGGCACTTCATATCATGCTGTCCCAGCTGA
CTTTCATCTTTGGGATTATGATTAGTTTCCATGCCGGTCCCATCTCCTTCTTCTATGACATAA
TTAATTACTGTGTAGCTCTCCCAAAAGCGAATTCCACCAGCATTCTAGTATTTCTAACTGTTG
TTGTTGCTCTGCGAATCAACAAATGTATCAGAATTTCTTTCAATCAGTATCCCATTGAGTTTC
CCATGGAATTATTTCTGATTATTGGCTTCACTGTGATTGCAAACAAGATAAGCATGGCCACAG
AAACCAGCCAGACGCTTATTGACATGATTCCTTATAGCTTTCTGCTTCCTGTAAC

FIGURE 444

ACAGTTGTGGGGAATCACTGTTCCTGGTTAGAAATTTCTGCATTTTATATTATTTTCTTGGCT
ATATTCCCAAAGCTTGGATTAGCACTGCTATGAACCTTCACATAGATGAGCAGGTTCATAGGC
CACTTGACACAGTGAGTGGCCTCTTAAATCTCTCGTTACTCTACCATGTCTGGCTGTGTGGTG
TCTTTCTCCTGACGACTTGGTATGTCTCATGGATACTCTTCAAAATCTATGCCACAGAGGCTC
ATGTGTTTCCTGTTCAACCACCATTTGCAGAAGGGTCAGATGAGTGCCTTCCAAAAGTGTTAA
ATAGCAATCCTCCCCCCATCATAAAGTATTTAGCCTTGCAGGACCTGATGTTGCTTTCTCAAT
ATTCTCCTTCACGAAGACAAGAAGTTTTCAGCCTCAGCCAACCAGGTGGACATCCCCACAATT
GGACAGCCATTTCAAGGGAGTGTTTGAATCTTTTAAATGGTATGACTCAGAAACTGATTCTCT
ATCAAGAAGCTGCTGCTACGAATGGGGGGCATCATGCGGCCGC

FIGURE 445

TTCATGGTAAAAAATGAACTACCCTCTGCCATAAAGTTTNTAATGGGAAAGGAAGAGACATTT
TCAGCNTGGACGTGGATGGCCGCGTTCTGGTGGTGATAGTTACCTTTGGCATAATTCTCCCTC
TGTGTCTCTTGAAGAACTTAGGGATCTTGGCTATACTAGTGGATTTTCCNTGAGCTGTATGGT
TTTTTTCCTAATTGTGGTTATTTACAAGAAATTTCAAATTCCCTGCATTGTTCCAGAGCTAAA
TTCAACAATAAGTGCTAATTCAACAAATGCTGACACGTGTACGCCAAAATATGTTACCTTCAA
TTCAAAGACCGTGTATGCTTTACCCACCATTGCATTTGCATTTGTTTGCCACCCGTCAGTCCT
GCCAATTTACAGTGAGCTTAAAGACCGATCACAGAAAAAAATGCAGATGGTTTCAAACATCTC
CTTTTTCGCCATGTTTGTTATGTACTTCTTGACTGCCATTTTTGGCTACTTGACATTCTATGA
CAACGTGCAGTCCGCGGCCGC

FIGURE 446

GNCCACACTGGCCAAAAGGTTGCCGCTAGCCGCCTGGGAATTTAAGGGACCCACACTACCTTC
CCGAAGTTGAAGGCAAGCGGTGATTGTTTGTAGACGGCGCTTTGTCATGGGACCTGTGCGGTT
GGGAATATTGCTTTTCCTTTTTTTGGCCGTGCACGAGGCTTGGGCTGGGATGTTGAAGGAGGA
GGACGATGACACAGAACGCTTGCCCAGCAAATGCGAAGTGTGTAAGCTGCTGAGCACAGAGCT
ACAGGCGGAACTGAGTCGCACCGGTCGATCTCGANAGGTGCTGGAGCTGGGGCAGGTGCTGGA
TACAGGCAAGAGGAAGAGACACGTGCCTTACAGCGTTTCAGAGACAAGGCTGGAAGAGGCCTT
AGAGAATTTATGTGAGCGGATCCTGGACTATAGTGTTCACGCTGAGCGCAAGGGCTCACTGAG
ATATGCCAAGGGTCAGAGTCAGACCATGGCAACACTGAAAGGCCTAGTGCAGAAGGGCCCTGC
GGCCGC

FIGURE 447

AAGTTTTTTTTAATTATCATGGGACGGGTTNTGGATTTAATGGGGGGAAAAGGGCGGAAAAG
GACAAGGATCCAAACTGGGGAATTTGTTGATNTTNGGGTCCCTNTCCGCTTTCCGGCCGGCAG
CGGCTGCCAGGGTATATTTCCTTTTTTCCGATCCTGCAACAGCCTCTTTAAACTGTTTAAATG
AGAATGTCCTTGGCTCANAGAGTACTACTCACCTGGCTTTTCACACTACTCTTCTTGATCATG
TTGGTGTTGAAACTGGATGAGAAAGCACCTTGGAACTGGTTCCTCATATTTATTCCAGTCTGG
ATATTTGATACTATCCTTCTTGTCCTGCTGATTGTGAAAATGGCTGGGCGGTGTAAGTNTGGC
TTTGACCCTCGACATGGATCACACAATATTAAAAAAAAAGCCTGGTACCTCATTGCAATGTTA
CTTAAATTAGCCTTCTGCCTCGCACTCTGTGCTAAACTGGAACAGTTTACTACCATGAATCTA
TCCTATGTCTTCATTCCTTTATGGGCCTTGCTGGCTGGGGCGGCCGC

FIGURE 448

TAATTAAAATGCACACACACACACACACACACACAGAAATTTTGAGAGCCATTTTAATATAATTG
CCTCCCTAGAAACATACCTTTTAGGGAATTTTTATCACTAAACCACATGTTATTTAAATACGT
ACATGTTTAACATAAATACATACATAAAATTCACATGCATACTTAACACTTATGTTAAATATA
TTCAATGTATATACATATGTACACAATATATGCATATATACATGTGGGTATGTGGTATGTGTG
CATGTGTGTGTATGGCCAGCTACATAATTTGTGGGACTAAGGGCAAAATGAAACTGTACGGCC
CTCGTTCAAAAATTAGGTGTGGGGCGGCCGC

FIGURE 449

CCAGTTTGTCAAACTACTACTCTTCAATGCTTCTACATAGCATTCTTTAAGGGCAAATTTGTA
GGCTATCCAGGAGACCCCAGTTTATTGGTTGGGAAAATACAGAAATGAAGAGTGTGACCCAGG
TGGCTGTCTTCTTGAACTGACAACTCAGCTTGACAATAATCATGGGAGGAAAAGCAATCTGGA
ATAACATACAAGAAGTATTATTGCCCTGGATCATGAATCTAATTGGGCGATTTCACAGAGTTT
CTGGATCAGAAAAGATAACCCCACGATGGGAACAGGACTACCATCTGCAGCCTATGGGCAAAC
TGGGATTATTTTATGAATATCTTGAAATGATTATTCAGTTTGGGTTCGTCACCTTATTTGTGG
CCTCTTTTCCACTGGCCCCTCTGTTGGCTCTCGTGAACAATATATTGGAAATAAGAGTGGACG
CATGGAAACTGACCACCCAGTTTAGACGCCTGGTACCAGAGAAAGCCCAAGACATTGGAGCAT
GGCAGCCCATCATGCAAGGAATAGCAATTCTGGCTGTGGCGGCCGC

FIGURE 450

CTGTTAATGATTGCATTTGGCCTTGCTGGGGGGGCATTTTCTTGCGGATCAAACCCNCGCAAA
GNGTNTTCATTTCCACGTGTCTGTCTTGTCAAGCACNCCCTTGGTGTCCAGGTTCCTTCATGG
CCAGTGCTCGGGGTACAAANAAGGCGACATTGANTACAAGCCCCGTGCTCNTCGGCATGCTGG
TAACNCAGGACGTGCAGCTCGGGCTCTTCATGGCCGTCATGCCGACTNTCATACAGGCGGGCG
CCAGTGCATCTTCTAGCATTGTCGTGGAAGTTCTCCGAATCCTGGTTTTGATTGGTCAGATTC
TTTTTTCACTAGCGGCGGTTTTTCTTTTATGTCTTGTTATAAAGAAGTATCTCATTGGACCCT
ATTATCGGAAGCTGCACATGGAAAGCAAGGGGAACAAAGAAATCCTGATCTTGGGAATATCTG
CCTTTATCTTCTTAATGTTAACGGTCACGGAGCTGCTGGACGTCTCCATGGAGCTGGG

FIGURE 451

ATCCCAGGCCTTTAGGCCCCGGAATNAACAATTGCAATGCACGTTTAAGGAAAAGGCCATNTC
GGATTCAGACCCTNACGGCCTTCCCACANTTTGTCNTCACTTGCAACAGGGCTTNGGGTGGGC
CTCCCGTTTNTAAAGCACCCCNCTATGAATGCACAGCAGGNCAANACCCAAGTCCCAAGACTG
CCTGGGCCTACTGGCCCCCCTAGCATTTGTGCAGAGGTNTCCTNTACAAGCTCCCATGTTGGG
AANAAGCACAGACCCACCAGGACCCCTGTTNTCCTCCTCAGATCCCCTTCCTGCCACCTTTTC
CCACTCCGGGGACTCAGCCCAGGACACCTCGNTGATTCCTGCCCCCTTTACACCTGCAAGCAG
GGATGCCGGCATCAGAAGAATGTTTNGTGTTTGAAATTGTTTGAGGGGTTTGGGTTTATTTTT
GTTGGTTTTTTCTTTTTTTTTGCTTANGTGGGC

FIGURE 452

ACGGCGCTCCCCGCCCGAAATCAAAGCTCCGAGTCATCCGTGTGGGGCATTCGTCCCCCCTGG
CACAGTTGGCCTCTTTCCAGAAGCCCGTTTTGTTTGTTTTACGTNTAAATTCGCGTCGGTTCT
TATTTCTCTCCCTGGCAAGGTCTGAANACGGGTAGGAGAATAACCTGTGTCAGCGTGTTATGA
TGCCGTCCCGTACCAACCTGGCTACTGGAATCCCCAGTAGTAAAGTGAAATATTCAAGGCTCT
CCAGCACAGACGATGGCTACATTGACCTTCAGTTTAAGAAAACCCCTCCTAAGATCCCTTATA
AGGCCATCGCACTTGCCACTGTGCTGTTTTTGATTGGCGCCTTTCTCATTATTATAGGCTCCC
TCCTGCTGTCAGGCTACATCAGCAAAGGGGGGGCAGACCGGGC

FIGURE 453

GTCATCTTTACATTCTAGTCCTCCTGCATCTCCTCAAGGTTCCCCTCACAAAGGTTACACACT
TATTCCATCAGCTAAATCTGNCAACTTGTCTGACTCCAGCCATAGTGAGATTTNTTCNCGGTC
CAGCATCGTGAGCAATTGTTCTGTTGACTCCATGTCTGCAGCTCTACAGGATGAACGGTGTTC
CTCTCAGGCCCTGGCAGTCCCTGAATCCACTGGGGCATTGGAAAAGACAGAGCACGCTTCAGG
GATAGGAGATCATAGTCAACATGGCCCTGGGTGGACACTCTTGAAGCCATCTCTAATCAAGTG
TTTAGCTGTCTCATCGTCTGTGAGCAATGAAGAGATTTCTCAAGAGCATATCATTATAGAAGC
AGCTGACAGTGGTCGTGGAAGTTGGACTTCGTGTTCAAGCAGCTCCCATGACAACTTCCAAAG
CCTTCCAAACCCAAAAAGCTGGGATTTTTTGAACTCTTACAGACATACCCATTTGGATGACCC

FIGURE 454

TTATGCTTTTCTTGCAGTATNTGAAAGGCCCGATTAACAAAACAANAGTCCCAANACCCCTTT
TCTTTTTTGGGTGTATCNCTAGNTGCAGGTGCTGTGTTCCTTAGTGTCATCTATTTGACTTAT
ACAGGTTACATTGCACCATGGAGTGGCAGGTTTTATTCATTGTGGGATACTGGGTATGCAAAA
ATACACATTCCAATTATTGCATCAGTGTNTGAGCATCAACCTACAGACTTGGGTGTCTTTCTT
CTTTGATCTACATATTCTTGTATGTACCTTCCCAGCAGGCCTTTGGTTNTGCATCAAAAATAT
CAACGATGAAAGAGTATTTGTTGCTCTATATGCAATCAGTGCTGTCTACTTTGCTGGAGTGAT
GGTGCGACTGATGTTGACTTTGACTCCAGTCGTGTGTATGCTGTCTGCAATTGCCTTTTCAAA
TGTTTTTGAGCACTATTTGGGGGGAGCGGCCGC

FIGURE 455

GCCAGAAAACCCTTAAGAAAAAAAGCGNAGGAAATTTTCGCCAAAGCTGAAAGATCNCAGCGG
CCTGAGAAAAAAGTTTGCCCCAAAAAGNNTGTTTNNAAAAGGCCAAGGAGGAAGCCCCCTTTT
NTCCCTNGGGCACTTGTATTTTTTNAACCCTGCTTTCCCCAAATCCCCACTNATGAGGATCAG
CCCATGGTGGTATTTTTGCGATGATTTCCTGNGTCCTGGAGTCTTTNTCNGGTCAACGGTTTT
CTTGTTATATTTGCNCTATGTAGCTGATGTCAATTCAGGAGCNCGGAGNGAAGTACAAGCTTA
TGGATGGGTNCTCAGCCCACCTTTGCGGCTAGTNCTTGTCAGCAGCCCGGGCCATTGGAGCAT
ATNTTTTCTGCCAGTTTNCGGAGACAGCCTCGTTGTGCTGGTGGCCCNCAGTGGTGGCTCTTN
TGGACATCTGGTTCATCTTAGTGGCTGTTCCAGAATCCTNTGCATGAGAAAATGAGNCCNGGT
TTCCTGGGGAGNTGCGGCCGC

FIGURE 456

TCCTTGTTAAACATGAAGGGCCCCGGTAGCCATGGTTTGGCCACCTTCATTCCAAGCACCCCG
CCCCAGCAAGGCCTCCTGGTACCTTTGTCANCCACTTGTTGTAGAAGGTGATGCCGATGGAGA
AGCAGTAGTAGANAAGCACCAGCCCCAGGGTCAACNCCGCCTTCCACAAAAAGCCACATCGAG
GGCCCNCCTCCCCATTCGTGGCGGCTGCAGCACCGGAGCTCCTGAGTCAGCGGGGGCAGGCAC
CCCTNTTGAATACAATGTGCAGGAAGAGCCGGTGGAGTTAGACCACAGCTTTCACCAAGAACG
TCTCCAGGCTGGAGGAGCTCTCTGCAGCTCCATGATTCGGAACCATCAGCAGAGCCCCAGGCA
GAGTCCTCACCTAAGGGGCTGGTGGCTGGTGCTGACCCTTCCCATGGTTAATTGGATGCAGCG
CTCACAGGTCCCAAGGTCTGCTCGGCCCTGGGAGCTCCAGGCCGGAATTTTTGGCCAGTGTGGCC

FIGURE 457

TGCTCCCCTCTCTCCTCTCCACAATCTCACCCATTNTGCATGTGCCGGTGCCCTTTCCTGTCA
TCCCACCTTTCTCTGAGACTGTGTTCTTTTTTCTTAATTCTGTTTTCTGTTTGTTCTTTAGGT
TGCATAGTCTTTATTGATATTTCTTTGAATTCACTGATTCTTCTGCCAGCTCAGTCTGTTGTT
GAGCC

FIGURE 458

GATTACAAAAACAAAAAATGTTTAATTTAAGTGAAAGGGNTTAATAATTTTAATCTGGGANTT
AATAATTCAGTGGAAATTTTAAATGAATAGTTACTATAATCNCAAATAATTGAGAGTCAACTT
TNTTTTTCCCCAAAACATACATGAAAGGTCTGTGTGTGTAAGCTCTGATTTTCAGGACCCCTA
TTTNTGGAAGCAGAGTAACTGGAAATANTAAGTCAAGATNTGAAAACCATTTGAAGTTAACCA
AAAAGCACAGGCTACTAAGGCAGGTGCAGCATCAATGATTCACTACATGGTTCTGATATCAGC
TCGCTTGGTACTACTCACTTTGTGTGGATGGGTACTTTGTTGGACCCTCGTCAATCTCTTTCG
AAGCCATTCAGTCCTCAATCTCCTTTTCCTTGGCTACCCGTTTGGTGTTTATGTTCCTCTTTG
CTGTTTTCATCAAGATAGTAGAGCACATCTTCTTCTCAC

FIGURE 459

CGGTCCGAATATCCGGAACCTGACCCAATCCTTGGCCTTTGAAACTTTCATTTTTTNGTTGTC
TGCCTCAACNCGTCAGGTGGNGCCCAAACNTTGGTAAAGTCNAGATCCGGGGGAGGGTACTTC
ATGGCCTTGGACTCCATATTNTTNTGCATNTACGTGGTGAAAGCCCTGCTCAAGATCATCGCC
CTGGGCCTCTTGGTACTTCTTTGACTTCTGGAACAATTTGGACTTNTTCATTATGGCCATGGC
CGTGCTGGACTTCTTGCTGATGCAGACCCACTCCTTCGCCATCTACCACCAAAGCCTCTTCCG
GATCCTCAAGGTCTTCAAGAGCCTGCGGGCCCTGAGGGCAATCCGGGTCCTGCGGAGGCTCAG
CTTCCTGACCAGCGTCCAGGAAGTGACAGGGACCCTGGGCCAGTCCTTGCCGTCCATCGCAGC
CATCCTCATCCTCATGTTTACCTGCCTCTTCCTCTTCTCCGCGGTCCTCCGGGCACTGTTCCG
CAAATCTGACCCCAAGCGCTTCCAGAACATCTTCACCACCATCTTCACCCTCTTCACCTT

FIGURE 460

CAAAGAAAAGAAAAGGGCACTTCGGAGCAAATCATACACTAGGCCTTTGATGCTTTAATTCTT
CTTCAGTTCATTAAAAGTAACTACTAAGGAAAGGTTAAAAACTTCCCCTCAAAAAGGAATCAA
CCCCAGGAAGTAATCATTTACAACGATTTTCCCAAATTTTGACAATCTGTCCTGGAAAGCAAA
CCCCTTTTAAAATCTAATGTCTGGGCTTTGAGTATTAGCTCATTTAGGGTGGACAAATGCATT
ACTGTTTTCAAACTGCTCACATTTATTCAGTATTTCTCCAAGTTGCTATCTACTCAGCCTTAT
GAATGCCCCTCGCTTTTCTAAGGCCATGTGAAAATCACGGCACTGCCCTTAGCCTTGTGTCAT
CTGCTTTTTCGTTCTGCGATATGCCCAGTTCCCAAATCAATTATAGGTACCTGTTTAGGAGAG
AGGAAGATTTTACCTCTCAAAGGGTGAGATTTGAAATTTACACTAAAAAGACAACTTTACATT
TAATGCTTCACTTAATGAGACATTCTTTTTTTTATAAGTCTATTTTTCTACTCAGTTTCAG

FIGURE 461

ATGCAGTTGTTAAGGTTTACTGCCCTTGCCATTTTAATTATGAGGCTAAAGATGTTTTTGACG
CTGCACATGTGTGTATGGCTTCCTTGATATGCTCTCGCAGTTCTTTGGTGGCTTTTTCGCAGA
GTTCGTTTTGATAATGTTATCTTTGGCATTCTAACAGTGATGTCAATACAAGGTTATGCAAAC
CTCCGTAATCAATGGAGCATAATAGGAGAATTTAATAATTTGCCTCAGGAAGAACTTTTACAG
TGGATCAAATACAATACCACATCAGATGCTGTCTTCGCAGGTGCCATGCCTACAATGGCAAGC
GTCAAGCTGTCTACACTTCATCCCATTGTGAATCATCCACTTTACGAAGATGCAGACTTGAGG
GCTCGGACAAAAATAGTTTATTCTACATATAGTCGAAAATCTGCCAAAGAAGTAGGAGAGAAA
TTGTTGGAGTTACATGTGAATTATTATGTTTTAGAAGAGGCATGGTGTGTTGTGAGAACTAAG
CCTGGTTGCAGTATGCTTGAAATCTGTGATGTGGAAGACCCTTCCAATGCAGCTAACCC

FIGURE 462

GAAGTGGGCCCAACATNTGACAAAACTCCCAATGAANGATTCCCCGCTTGAAACAATGGGGGC
AGGGCTNCCGGCTTCGAGGGGCAAGTTTCAAGCATTCAACAAAGGGTCCCCCGGAAAATTTCN
ANGGNGTCCAACACTCAGTGCCCNCAGCCCAGCCNCAGAACCCAANACATAAGGCATGTCATC
CACAAGCTCTCCTTTGGGGACAACGCTACAGGTCCAGAACATCCNCGGAGCTTTCAATGCTCT
CGGGGGAGCAGACAGACTCACCTCCAACCCCCTGGCCTCCCACGACNTACATCCTGAAGATTG
TGCCCNCGGTTTATGAGGACAAGAGTGGCAAGCAGCGGTACTCCTACCAGTANACGGTGGCCA
ACAAGGAATACGTCGCCTACAGCCACACGGGCCGCATCATCCCTGCAATCTGGTTCCGCTACG
ACCTCAGCCCCATCACGGTCAAGTACACAGAGAGACCTGCGGCCGC

FIGURE 463

TATCAAGGGGCGGGTTTTGGATTTAATGGGGGGAAAAGGGGGGAAAAGGCCAGGATCCNAACT
GGNGAATTTGGTGATTTTNGGGTCCCTTTCCGCTTTCCGGCCGGGAAGGGCTGCCAGGGTATA
TTTCCTTTTTTCCGATCCTGCAACAGCCTCTTTAAACTGTTTAAATGAGAATGTCCTTGGCTC
AGAGAGTACTACTCACCTGGCTTTTCACACTACTCTTNTTGATCATGTTGGTGTTGAAACTGG
ATGAGAAAGCACCTTGGAACTGGTTCCTCATATTTATTCCAGTCTGGATATTTGATACTATCC
TTCTTGTCCTGCTGATTGTGAAAATGGCTGGGCGGTGTAAGTCTGGCTTTGACCCTCGACATG
GATCACACAATATTAAAAAAAAAGCCTGGTACCTCATTGCAATGTTACTTAAATTAGCCTTNT
GCCTCGCACTCTGTGCTAAACTGGAACAGTTTACTACCATGAATCTATCCTATGTCTTCATTC
CTTTATGGGCCTTGCTGGCTGGAGCGGCCGC

FIGURE 464

AAAAGGCCAATTTTAAGCAAAATATAACAAAACGAGAAGTGGAGGATGACTTGGGTNTNAGCA
TGCTGATTGACTCCCAGAACAACCAGTATATTTTGACCAAGCCCAGAGATTCAACCATCCCAC
GTGCAGATCACCACTTTATAAAGGACATTGTTACCATAGGAATGCTGTCCTTGCCTTGTGGCT
GGCTATGTACAGCCATAGGATTGCCTACAATGTTTGGTTATATTATTTGTGGTGTACTTCTGG
GACCTTCAGGACTAAATAGTATTAAGTCTATTGTGCAAGTGGAGACATTAGGAGAATTTGGGG
TGTTTTTTACTCTTTTTCTTGTTGGCTTAGAATTTTCTCCAGAAAAGCTAAGAAAGGTGTGGA
AGATTTCCTTACAAGGGCCGTGTTACATGACACTGTTAATGATTGCATTTGGCTTGCTGTGGG
GAGCGGCCGC

FIGURE 465

CACTGGCCAAACCATTATATGGCATACTCTGGNTACGTGGTCTGCCTGTTATTGGAAAGATAT
ATTAAGAATCCAGTTNTGGATTGCAGCTGTTATTTTTTTGGGAATGCTTGAAAAAGCAGTTTT
TTATAGTGAATACCAAAACATCAGCAACACTGGACTGTCAACCCAAGGCTTATTGATATTTGC
GGAGTTGATTTCTGCGATTAAGAGGACGTTGGCTCGCCTTCTCGTGATCATTGTGAGCCTGGG
CTATGGCATTGTGAAGCCTCGTTTAGGAACAGTCATGCACCGGGTGATCGGACTGGGGCTTCT
ATACTTAATCTTTGCAGCTGTTGAAGGCGTGATGAGAGTCATTGGGGGTTCTAACCATTTAGC
TGTTGTTCTTGATGACATTATTTTAGCAGTTATTGACTCCATTTTTGTGTGGTTCATTTTTAT
TAGTTTGGCACAAACTATGAAGACCCTAAGGCTAAGAAAGAACACTGTGAAATTTTCATTATA
TAGACATTTTAAAAATACTCTGATCTTTGCTGTGCTGGCTTCTATAGTGTTTATGGGGTGGGC
GGCCGC

FIGURE 466

TGGATGGTACCCTGGCCCNTCCAGAGTCCCAGGGCAATGGGTCCATTTTCAGCCCAATGTGGT
GTACATTACCCTACGCTCCAAGCGCAGCAAGCCGGCCAATATCCGTGGCACCGTAAGCCCAAG
CGCAGGAAAAAGCATGCAGTGGCATCGGCTGCCCCAGGGCAGGAGGCTTTGGTCGGACCATCC
CTTCAGCCGCAGGAAGCGGCAAGGGAAGCTGATGCTGTAGCACCTGGGTACGCTCAGGGAGCA
AACCTGGTTAAGATTGGAGAGCGACCCTGGAGGTTGGTGCGGGGTCCGGGAGTGCGAGCCGGG
GGCCCAGACTTCCTGCAGCCCAGCTCCAGGGAGAGCAACATTAGGATCTACAGCGAGAGCGCC
CCCTCCTGGCTGAGCAAAGATGACATCCGAAGAATGCGACTCTTGGCGGACAGCGCAGTGGCA
GGGCTCCGGCCTGTGTCCTCTAGGAGCGGAGCCCGTTTGCTGGTGCTGGAGGGGGGTGCGGCCGC

FIGURE 467

AACCTGTGACGTTAGTGTGTTCTTACTAGCTTTAATTTGTATGTAGCAATGAATTGTGAATCT
TAGTGCAGTGGGTTTTTTTAAAAAACTCAAAAAGCTGGGAATTAAGGGTTTCAGTAATAATGC
TATACCGAGGTGCTTGCATTGTATTTCATAATTTTGTTACAAACCAAAATTATTTTTAATGAG
AACAGTCTTGGGTTCAGAGGTGTGATGCCAGAATGTATTTTCGTACTGTTAGGCCCTTGGAAC
AGATACCGGTGCTTTCTGAAAGATGAAAGAAATGCAATGGGTGCTCTTCATGCAAGGTTGCAA
ACCTACCAAGAATGCATAATAGTCTCACTTTTCCCCAATAAAGAGATGCGTGTGACTAGTTTT
GGACTTTTAACCTTAATGGGGATGGCGGCCGC

FIGURE 468

ATGGTCCTGGGCATCCATTGACCTGCTTTCTGTCCCTGTAGATTAGTTTTGCCTGTTCTAGAA
TTTTATGTATGTAAGGGAATGATGACTATGTATGTTTGTGTTTGGCTTATTTTTACCAGCAAG
TTTTTGAGGTTCATGTTATTGTGTGTATCAGAAGTTAGTTTCTATTTATTGCTCAGTAGTATT
TCATTCTGTGAATTTACCATGGTCTGTTTAATATATTCATCTATTGATGATGAACATTTAGAT
TACTTTTCGTTTTTGCCTATTAAAAATAAAGTTAGTATGAATATGCATGTACAAGTTGTATTG
TGGATATACTTTGTGATAATAACTAGAACCAGGAGTGGTTCAAAATTTAATTTACACATCTAC
TCCCTGTGTTATTTGCC

FIGURE 469

TGGCTGAAAATTTTTGGAAAAAAGAATATTTTCTTTTTAATAGGTAACTTAANATATTTTATT
CATTGTCGCCCAGTGTAACAAGAGGAATCAGTTAAACTCCTGTGTCCAGGCCAGTACCNCCAA
TTAATGCACTTGTAGCTACTGAATTCCAGCCAAGATAAATATAATTAAATCTAGTGCTTCAGG
AAATGAGTTGATCATCAAGGGAGTTAGAATGGAAAAACATTTATGNATAATTTTAAAGGACAT
TGGACTTAACTGTTTGGAATGAATGAGCTTGATTTTTTCTATACATATTATAAGTTAATATAA
AAAAAGGCTTTGGGTAGACTCCGTATGACCTTATGTATTTGATTTCATGAGTTTCATTTTCTG
CAGTAACTTTATCATTCATTTTTCATCTCTTAGGCTGGAATGTAGTGGAAAAAGAACTGAACT
AGGAGTTAGAAGATTTAAGTTTTGGCTCTGGCTCCATCACATACTGGCAGTGATGATCTTAGC
CAAGTTTGAACTGCTTATGGCGGGGTCTTGTTTATTCATTTCAGTATTTCCAAC

FIGURE 470

AGTTACCCTCACTTTACCAAGGACTTTGCTCGGCGTTTATTAGTGCTGTTTGGGTAGCATTCC
CATTGCTCACAAAGCTCTGTGTGCATAAGGACTTCAAGCAGCATGGTGCCCAAGGAAAATTTA
TTGCTTTTTACCTTTTGGGGATGTTTATTCCTTATCTTTATGCATTGACCTCATCTGGGCAGT
ATTTGAGATGTTTACCCCTATCCTCGGGAGAAGTGGTTCTGAAATCCCACCTGATGTTGTGCT
GGCATCCATTTTGGCTGGCTGTACAATGATTCTCTCGTCCTATTTTATTAACTTCATCTACCT
TGCCAAGAGCACAAAAAAAACCATGCTAACTTTAACTTTGGTATGTGCAATTACATTCCTCCT
TGTTTGCAGTGGAACATTTTTTCCATATAGCTCCAATCCTGCTAATCCGAAGCCAAAGAGAGT
GTTTCTTCAGCATATGACTAGAACATTCCATGACTTGGAAGGAAATGCAGTTAAACGGACTC
TGGAATATGGATCAATGGGTTTGATTATACTGGAATTTCTCACATAAC

FIGURE 471

GAGGCATTGTGAATGGTTGCAGTGNAGCTTAGGTATAACATCATCAAGTGTGTTCACACGCGG
GGTCGGGTTTAATGGAGTGTCCACGCGGAGATAACTGCGATATTGGAACACCTGTGAGAGAGA
TTGTTCTATAGGGTGGAATATTCAGAGTTACATTCTTGGAAGTTTCTGTTTTTACTTGCATCA
AACACCCCTCTGTTGTTCTCCATCATCTTTAATAGCAACTGGAGACCACTTTGGTCATTGGTA
AGGGGGTGCATTCTCCTCACAAAGGGGTTTTATGGACTTCCTCAGGCGGAGAGCTTCTGAGAA
CACAGGCAGGATGGAAAAAGACTACTAGCCACTTTTGCTTTCCCAACCCCCCTTAATGCCATC
CTTCATTGTCTTTCTGGCTTCTCTTCTTCTGGCACAGTACCATTTTGGGTCTGTGCCCCAGTG
TGGAGCAAAACATTGCCTGTCCCATTCTGATATACTTCAGAATTTGAGAGCAGAAGTTAATGT
GGAACAAAAGTTTTCACCATCTCTCAAGCCCCAAGGACTGGAGCC

FIGURE 472

ATTAGGCTGTTTGGGAGCATTCCCATTGCTCACAAAAGCTTTGTGNGCATAAGGACTTCAAGC
AGCATGGGCCCAAGAAAATTTATTGCTTTTTNCCTTTTGGGGATGTTTATTCCTTATCTTTAT
GCATTGTACCTCATCTGGGCAGATTTGAGATGTTTACCCCTATCCTCGGGAGAAGTGGTTCTG
AAATCCCACCTGATGTTGTGCTGGCATCCATTTTGGCTGGCTGACAATGATTCTCTCGTCCTA
TTTTATTAACTTCATCTACCTTGCCAAGAGCACAAAAAAAAACCATGCTAACTTTAACTTTGGT
ATGTGCAATTACATTCCTCCTTGTTTGCAGTGGAACATTTTTTCCATATAGCTCCAATCCTGC
TAATCCGAAGCCAAAGAGAGTGTTTNTTCAGCATATGACTAGAACATTCCATGACTTGGAAGG
AAATGCAGTTAAACGGGACTCTGGAATATGGATCAATGGGTTTGATTATACTGGAATTTCTCA
CATAAC

FIGURE 473

GATTGCAAGGAGGATTTTATATGATAGTCATAGCTTGTCTTTAAAAGTTTGGTATGTGATAAT
ATCAGANCAGTAAAAGGCTATTTCACATTTTAAAACTAAATCTTTATTAAATAATTATTTCAC
AAGTTAGTAATTATTGATATTCTTCTTCAGGGACTAGAGTTCCTATGCTTCCTAAACTGACTT
TTAAGGAAAGATGAGACTATATTCAGTGCAGTTTTAATATGACATATTTTATTATCTCTTATT
TTTTAAATTGATATTTTATGAAGGAGTCTATGGACTATAATACGAAAATTCTGGTTGGGGAGG
CAGGAAACCTGGCTTTCAAGTACACTCCAATAGCTTTTATATAAAATTCAGGTGTTCTTTTTC
TCTAATACTTGAAATAGCTATTTTCATTTTCATGTCATTTTCTGTACTTTTCCTGATACTTTT
AAACATTGTTTTATTTTCAAATGAACAGCC

FIGURE 474

TTCCCGCAATTTTCAGAAAAAATGGGANTAAAAGAAACTATTTTGTAAAATAAAAAAGCTTCCA
TTTTTAATGACCANCATGTATTAAGATGGAACNTACTNTACGAAANCGAAGTTNTATGGTNTC
GAAAAGCCCGTGCCTGTTTAAAACTTGATCCTAACTAAAAACAGACTTGAGTGGATATNAGAA
TGTTGGTTAGTGGCAGAAGAGTCAAAAAATGGCAGTTAATTATTCAGTTATTTGCTACTTGTT
TTTTAGCGAGCCTCATGTTTTTTTGGGAACCAATCGATAATCACATTGTGAGCCATATGAAGT
CATATTCTTACAGATACCTCATAAATAGCTATGACTTTGTGAATGATACCCTGTCTCTTAAGCA

FIGURE 475

TTTAGAAATGGTATGGCAGAATCCAGAAAATGCTTTATTGAAGACAGTCATTGATCACCAGTA
CACTTGATCTCCAGTACAGACATATGGTGGAACAGAAGCCTGGATACAGGACTCAGACTCTTA
CTGGTTGGTATCATACGTGATCGTTTGATTCAGTTCATCTCTAAATTGCAGTTTGCCGTGACT
GTGCTTTTGACATCATGGACAGAGAAAAAACAACGTCGAAAAACAACTGCCACTTTATGTATA
CTCAACATTGTCTTTTCTCCATTCGTGTTGGTCATCATAGTTTTTTCTACACTACTCTCTTCT
CCCTTACTCCCTCTTTTCACCCTTCCTGTGTTCTTGGTGGGGTTTCCCCGACCTATTCAGAGT
TGGCCAGGAGCAGCAGGCACCACAGCCTGTGTGTGTGCAGATACAGTGTACTACTACCAAATG
GTGCC

FIGURE 476

GGGTGCTCTTTTTCAATTCAGGAACATCAACATTTANTAAACNGTGGGGTGGGATCCTTACAA
ATCATCCTGCTTTTTTGNANATCACTGGCTACTAAGGCAGGTGCAGCATCAATGATTCACTAN
ATGGTTTTGATATCAGCTCGCTTGGTACTACTCACTTTTGTGTGGATGGGTACTTTGTTGGAC
CCTCGTCAATCTCTTTNGAAGCCATTCAGTCCTCAATCTCCTTTTCCTTGGGTANCCGTTTGG
TGTNTTATGTTCCTCTTTGCTGTTTTCATCAAGATAGTAGAGCACATCTTCTTCTCACAGACT
ACAAATATGTGGTTCAGCACGAGGCAGTAGAGGAAAGTGCCTCGACTGTGGGAGGCTTGGCCA
AATCCAAAGACTTTCTCTCCTTGTTGCTGGAGTCGCTAAAAGAACAGTTTAATAATGCCACAC
CCATCCCCAC

FIGURE 477

GGCCACNCTGGCCAAATAAGGGCAAAAAGCTTTATTTTTTTGAACAGGAAAACATGTTTTTTA
AATTCACATGTTTTGTATGAGACTTTTGCGAAGCAAGGCATGAACTGCTAGGTATTATTAAGA
ATGAATGATTTTTGCATTTAAGTTGTTTGAAGGCATGTATTTTGAAAAATATCTGTTACAAAT
TTATAATTTCAAGACAAATTGAATCTTATTTTATAATACTTTTGGAATTTCATTAATAAGGCT
AAAATTTGAGGAATATAACTAATTTTCAGCCTTAAGACATTTAAGTTTGGAAGTCCTTGCTAT
TCAACAGAATAACAAGAAAACTTCAGAATGTATCACTCTCCTGAAAAGAAGATATTAATAAGC
CCTTTTATTTATGGTTATAGTTTTATTTATAGTCTCAAAATTCCTAAAGCAATGCTACAACCA
TTGAATTTGCCATATTTTGTATCAGTGCTGTTAATTTGCTGTTGCCTCAAGAAAAAGTGCTTT
TTCTCCATGGATGAGGCGGCCGC

FIGURE 478

CACACACACACACACACACAGAAATTTTGAGAGCCATTTTAATATAATTGCCTCCCTAGAAACAT
ACCTTTTAGGGNATTTTTATCACTAAACCACATGTTATTTAAATACGGTACATGTTTAACATA
AATACATACATAAAATTCACATGCATACTTAACACTTATGTTAAATATATTCAATGTATATAC
ATATGTACACAATATATGCATATATACATGTGGGTATGTGGTATGTGTGCATGTGTGTGTATG
GCCAGCTACATAATTTGTGGGACTAAGGGCAAAATGAAACTGTACGGCCCTCGTTCAAAAATT
AGGTGTGGAGCGGCCGC

FIGURE 479

ACCAATCAGATGTATTTAGGGATTTGGGATATTCTACCAGGTGTTGTGAAATGTCAAATGGAA
CAAGCGTTTCATCTTGATTTTGGAACTGAATTGGAACCAAGAAAAGAAATAGTGCTATTTGAT
AAGCCAACTAGAGGAACTACTGTACAAAAATTTAAAGAAATGGTCTATAGTCTCTTTAAGGCA
AAATTGGGTGACCAAGGAAACCTCTCTGAACTGGTTAATCTCATCTTGACGGTGGCTGATGGA
GACAAAGATGGCCAGGTTTCCTTGGGAGAAGCAAAGTCGGCATGGGCACTTCTTCAACTGAAT
GAATTTCTTCTCATGGTGATACTTCAAGATAAAGAACATACCCCCAAATTAATGGGATTCTGT
GGTGACCTCTATGTGATGGAAAGTGTTGAATATACCTCTCTTTATGGAATAAGCCTTCCTTGG
GTCATTGAACTTTTTATTCCATCTGGGTTCAGAAGAAGCATGGATCAGCTGTTCACACCATCA
TGGCCAAGAAAGGCCAAAATAGCCATAGGACTTCTAGAATTTGTGGAAGATGTTTTCCATGGCCC

FIGURE 480

CCCGCCATGACTCGGAGACTGAGGACATGTATGGGACGACNTGCTACATGGCCCAGAGTGCCG
GTCATCTGTCACCAGTGACAGTGAGGGGGCCCATGTGAATACCCTTCACTCAGGGCCAAACGT
GCCCCAAAGAGGATGTTTTTCAGCAGAATCATTTATTCTGGCTTCAGAATTCAAGTCCTTCCT
CTGATCGAGTTAGGCAATAATCTGGGAGGGGAATGAGTGCAAAAAGATGGATATGTCTGTGTT
GGAAATAAGTGGCATCATCATGAGCAGGGTCAATACCTATCAGCAAGGAGTAGGTTATCAGAT
GCTGGGAAATGTTGTCACTATTGGATTAGCATTTTTTCCATTCTTACATCGACTTTTCCGTGA
GAAGAGCCTTGACCAACTAAAGTCCATTTCAGCTGAGGAGATCTTGACTCTCTTTTGTGGGGC
ACCACCTGTTACACCTATTATTGTTTTGTCGATAATTAATTTTTTTGAAAGATTGTGTCTTAC
TTGGATGTTTTTTTTCATGATGTGTGTGGCGGCCGC

FIGURE 481

GGCCACACTGGCCAAAGAGCATATTTGATCACTTTGATTCTCTGTTCTTTTCTCTCCGCGGTG
TGTGTGGCGGCCGC

FIGURE 482

AAAGACCCAGTCATGGCAAGCCTCCAAGCATCAGTTCACCATGGGGAAAGCATGTGTTCAAAG
CCATTCTGATGGTCCTAAGTGGCCCTTATCCTCCTCCACTCAGCATTGGCCCAGTCCCGTCGA
GACTTTGCACCACCAGGCCAACAGAAGAGAGAAGCCCCAGTTGATGTCTTGACCCAGATAGGT
CGATCTGTGCGAGGGACACTGGATGCCTGGATTGGGCCAGAGACCATGCACCTGGTGTCAGAG
TCTTCGTCCCAAGTGTTGTGGGCCATCTCATCAGCCATTTCTGTGGCCTTCTTTGCTCTGTCT
GGGATCGCCGCACAGCTGCTGAATGCCTTGGGACTAGCTGGTGATTACCTCGCCCAGGGCCTG
AAGCTCAGCCCTGGCCAGGTCCAGACCTTCCTGCTGTGGGGAGCAGGGGCCCTGGTCGTCTAC
TGGCTGCTGTCTCTGCTCCTCGGCTTGGTCTTGGCCTTGCTGGGGCGGATCCTGTGGGGCCTG
AAGCTTGTCATCTTCCTGGCCGGCTTCGTGGCCCTGATGAGGTCGGTAGCGGCCGC

FIGURE 483

CAAAACGATTTTATTGCCAAACCCTGTGCACTCCGATTGGCATCGAGGACAGTGGTCCTTATC
AGGCCCAACCCAATGCCATCCTTGAAAAGGTGTTCATATCTATTACCAAGTATCCTGATAAGA
AAAGGTGNAGGGCCTGTCAAAGCAGCTGGATTGGAATGTCCGAAAAATCCAATGCTGGTTNGC
CATCGGAGGAATCAGGACAAGCCCCCAACGCTTANTAAATTCTGTGAAAGCATGTGGAGATTC
ACATTTTATTTATGTATATTCTGCTATGGAATTAGATTTCTCTGGTCGTCACCTTGGTTCTGG
GACATCCGACAGTGCTGGCATAACTATCCATTTCAGCCTCTTTCAAGTGGGCTTTATCACTAT
TATATCATGGAATTGGCCTTCTATTGGTCCCTTATGTTTTCTCAGTTTACAGACATTAAAAGA
AAGGACTTCCTGATCATGTTTGTGCATCACTTGGTCACCATTGGGCTTATCTCCTTCTCCTAC
ATCAACAATATGGTTCGAGTGGGAACTCTGATCATGTGTCTACATGATGTCTCAGACTTCTTG
CTGGGGGCGGCCGC

FIGURE 484

TCTAGGTCCATTGTCACCTTTTCTGGCACGACAGCCTCCGCCCCACCGCATTCCCCAGGCCAA
GCTGGTGGCCATGCTTCAGACACGAGACCCACCAAGGGCCTCCGCCAGACCACGGTGCCTGCC
AAGGGCCACCCTGAGCGCCGGCTGCTGTCAGTGGGGGATGGGACCCGTGTTGGGATGGGAGCC
CGAACCCCCAGGCCTGGGGCGGGCCTCAGGGACCAGCAAATGGCCCCATCCGCTGCTCCTCAG
GCCCCAGAAGCCTTCACACTCAAGGAGAAGGGGCACCTGCTGCGGCTGCCTGCGGCATTCAGG
AAAGCAGCTTCCCAGAACTCGAGCCTGTGGGCCTAGCGGCCGC

FIGURE 485

CTGGCCAAACATATGGGGGATGAAAATAAAANAATTACATATGAAGATTCAAAACCATCCNCA
GGAATGAATTACACGCCCTCCCAGGCATCAANAAGCNCAGGAGGAGNCAGTTATGAAGTCAAA
GGTATAGATGCAAAATGAACCAACAAAAGGAAGTTTTTTTTTGAAAAGCAGTAAAAAAAAGCT
NCAAGAAACACCCAANTGAAGCAAATCACGTACAAAGANTGAGACAAATGCTGGCTTGCCCTC
CACATGGTTTACTGGACAGGGTCATAACAAATGTTACCATCATTGTTCTTCTGTGGGCTGTAG
TTTGGTCAATTACTGGCAGTGAATGTCTTCCTGGAGGAAACCTATTTGGAATTATAATCCTAT
TCTATTGTGCCATCATTGGTGGTAAACTTTTGGGGCTTATTAAGTTACCTACATTGCCTCCAC
TGCCTTCTCTTCTTGGCATGCTGCTTGCAGGGTTTCTCATCAGAAATATCCCAGTCATCAACG
ATAATGTGCAGATCAAGCACAAGTGGTCTTCCTCTTTGAGAAGCATAGCCCTGTCTATCATTC
TGGCTCGTGCGGCCGC

FIGURE 486

TGCATCGTGGGGTATGTACAATGTTTACGCATGTGAGTGTGTGTAAAGTGTGTGTATNAAGTG
TGTGTGTACATCTGTGCAGCTGGTCACCAGCATGTACCTTCACAAGTTAGATTTTGCTGGCAT
ATCCACGAGCTGTCACCACTGTGCCNTGGGCATTGAGCTTTTTGAGGCTTGTGTGTTGGCCTG
TCCCAGGGCTCTGCCATCGTCAGTATTGGCCCCACTCACAGATGTTCTTTCCTGGGTTGGGCC
AGCTCCTTTTGGACACTTTTGAGATCCACCTCGGGCCCGTCTGCGTTTGCGATGCTGCTTTTN
TGTGGCTCCTTCCGGCTACTGGGACTGTTCCCTTCTGGCATTGCCTTCGGCAGCACTTCGAGG
AACTCAGCCTCCAGGGCCTCCTGTTGTCCTTGAAAATGCAGTTTTATTTCATTATTTTTATTT
ATTTATTTTTGGG

FIGURE 487

CTCAAAATTAAAGTATCAAACAGGGGTCCTCAGAACTGTCTCACTTCCTCCTGCTCCCATCAA
TATTAAAGCCTAAAACTCAAGAATCATTCTTAGCAGTTTTTTTCTCTTTTTTCTTTCTTTTCT
TTTTTTTCTTTTTTGAGACGGAGTCTCACTCTGTCGCCCAGGCTGGAGTGCAGTGGCGACAGA
GTGAGAC

FIGURE 488

GTGTGTGAGTGTGTGTGTGTTTAATGTACCTAATTCTGTAAAGGATTTTAAGTGATTTTTTCA
AAGTGGACCCAATAAAATAAAAACAATATGCGTGCATGTGTTTTATAAAAGTAATAAAACNAG
TTATTCTGCTTTTTCTAGTCTTAGTTACTTACTTACATATTTATTTGGGGGGTGTGATGTTCT
TTTTAAAAGGAACTCCTGTGACACCTGTTACTCCGGC

FIGURE 489

GCAGCTGCCTATTGCACTTGTGAAAAAGGTTTGTATGTTCAACACTGCTGGGNTGGCTCANAG
TTGGGAGTGAATCCTCCAAGGGATAAGCTTGGAGAACTTTTTGAACAGTCAATCTGTAAAGGT
GTTTGCAATCCCAAGGNCAATGGACTAGATTATGAAGGCTCTCGGGTGGACCCACTGTTCCTC
TCTGTTTATTAAGCTTTTTGAAGGAGAGAGATGAGGGCAGGACATGTGACAACGGTGCTTTTC
CTTATGCNTATATCGCTCTCCAACAGCATCCTTTCCAAATNTATAGCGCTTCAAAGATTCCAG
GACAGATCGGGAAGAGCCAGTGTCCATAGAAACCTGGGGTTGTTCAGAAGAACGGTGTTCTCT
GTGTTTGTGACGGTGCCTGT

FIGURE 490

GGTTTTGTCCTTCGGTATGACAACTACAAAAAAGCAAGCCAGTGGGGATTCNTGTGGGGCCCN
TGGACCTGCCAAACATCTCCGGGNGCATGCAAAAAGGTCTCCTACTTTCACTGCACCCTCATC
GGATACTTTGTAGGCCTGCTCACTGCTACTGTGGCGTCTCGCATTCACCGGGCCGCCCAGCCC
GCCCTTCTCTATTTGGTGCCATTTACTTTATTGCCACTCCTCACGATGGCCTATTTAAAGGGC
GACCTCCGGCGGATGTGGTCTGAGCCTTTCCACTCCAAGTCCAGCAGCTCCCGATTCCTGGAA
GTATGATGGATCACGTGGAAAGTGACCAGATGGCCGTCATAGTCCTTTTCTCTCAACTCATGG
TTTGTTTCCTCTTAGAGCTGGCCTGGTACTCAGAAATGTACCTGTGTTTAAGGAACTGCCGTG
TGACTGGATTTGGCATTGAAAGGGAGCTCGTTTGCAGGAGAGAGGTGCTGGAGCCCTGTTTGG
TTCCTTCTCTTCCTGCGGATGTAGAGGTGGGGCCCCTTCCAAGAGGGACAGGCCTCTCCCCAGC

FIGURE 491

AAGACTCCCAAGGAAGTTGTTGAACTATATTTGGANAAACANGCCACTGAATATTATCATTTT
TCCTTTTAAANAGAGTTTTGTAAGGGGGNAAACATGCATTTTTATCCAGACAATTTATCCAAA
GCATTTCAGAACATGAAGTGCTGATGAGGGCACCTCTTGTGNTGAGTCCCNTAAGCTATCAAG
TGTTCTTCTCAAGGACACATTTGGAAGGTTTTAACATTGAAANTGAGCGGAGGACTTGGGGGC
AGAGCAGCACAAAGAAACAGCCTTACACTGGGCACATGGAGGAGACGTCCACCCTGCAGCCAG
GATTGGGGTTCACGTCACTGCCAGAGCTACACTCGCCTTCTGCTTCCACGGTCCTGTTAATTC
TAGATCAGAGAGCAAGAAAAAAGTACAGAACATATCCTCTACGGTTATTTCCTGCTTTCTAAT
TAAAAAAATAATAACCATGGCAAGAGAGAAAGAAAGAGAAAGTACTCAGAGGCTGACACTGAC
ATTTCACTTCCTCGCTCTCCTAAGTTTAATTACAACAGCACGTGCAGC

FIGURE 492

TGCAGCATTGGCAGCAACAAAAATTTCTAGTTTGGNTGATGATTTTGGAGAATTCAGCCTTTT
TGGGGAATATTTTGGTCTAGCACCTGTTGGGGAGCAGGATGACTTTGCAGATTTTATGGCTTT
CAGTAATAGCTTTATTTCATNTGAGCAAAAGCCGGATGACAAATATGATGCCCTTAAAGAGGA
AGCCAGTCCTGTTCCTCTAACCAGCAACGTGGGCAGCACAGTGAAGGGTGGACAAAACTCGAC
TGCTGCGTCTACCAAGTACGATGTCTTCAGACAACTTTCTCTGGAAGGGTCTGGACTAGGTGT
TGAAGACCTGAAAGATAACACTCCTTCAGGAAAAAGTGATGATGATTTTGCTGACTTCCACTC
CAGTAAATTTTCTTCCATAAACTCGGACAAATCCCTGGGAGAGAAAGCAGTGGCTTTCAGACA
CACCAAAGAAGACTCTGCATCAGTGAAGTCCTTAGATCTCCCTTCCATTGGTGGCAGCAGTGT
TGGCAAGGAGGACTCTGAAGATGCACTCTCTGTTCAGTTTGACATGAAATTGGCTGATGTGGG
AGGAGCGGCCGC

FIGURE 493

GCCCTATCCAGGTTACCCTTCCNAAGGGAAACCAGGTTTCTTTAAAAAATTAAGCAGCCCGGG
GCCGGTGGGCTCACGCTTGTAATCCNAGCCTTTGAAGCCCGAGGCGGCGGATCACCTAGAAGA
TGACTCAAGACCGGCCTCTGCTTGCCGTGCAGGAGGCGTNAAGAAGTGCTTCCCCGTGGTGGA
GANCAGCAGGGCCTGTGCAGAGTGCCCTGCGGGACTGCCAGCCCCTCCTGTCCTCCCTCAGCA
ACCTGGCGGAACAGCTGCAGGCCGCACAGAACCTGCGGTTTGAGGATGTGCCGGCGCTTCGGG
CCTTCCCAGATTTAAAAGAGCGGNTGAGGCGTAAGCAGCTGGTGGCTGGTGACATCGTCCTGG
ACAAGCTAGGGGAAAGGCTAGCCATCCTCCTCAAGGTGCGAGACATGGTCAGCAGCCATGTGG
AGCGAGTGTTTCAGATCTATGAGCAACACGCAGACACAGTTGGCATTGATGCTGTCCTGCAGC
CTTCAGCAGTGAGCCCCTCTGTGGCTGACATGTTGGAATGGTTGCTGGATATTGAGAGACGGG
CGGCCGC

FIGURE 494

CAGCATGAGACATCCCCCCATGCCTGGGGCCATTNAGATNTTTTTGGAGCACCAGTCACTCCC
AGGTTTTTATTTTAGGGGTCATCGATTTTACCTACTTTGTCAGACTGGTANAAGTTGCTTTGC
ATATCANAAAAACTCCATTTTTTTCCACAAAAGGGATTACAGAAAACTCTTTTGTGAGTGAGT
GATTGGAACTTAGAGACTCCTGTTGCCAGAATCAGACTGCCCTAGAACAGAATGGACAATGCA
GGGAGGAGAATTCACACAAACAGCACCTGTTNTGAGGCCTGTGCCAGCCCACCAGGCCTGCTC
AAATGTGGTCTTTACTTCAAGTGCACAGAGGCACATGAGGTTTNTGGTGATAAACCAGCGTCT
TACCGCTGTTTTAAAGTCCCATCCCCATGGCTTTCACAATCAGTTCCGTTTTTTTTGCTGTAC
TTGATAAAATGTTTATTCTCATACAGGTCAAGTACATTTACTTCTATTCACAGTGAGTACCCA
ATAACAACAAAAGCGCTTACAAATTTGGGGGGGGCGGCCGC

FIGURE 495

TTTTTTAAAAAAAAAAAAAAATCTCAGTATAGTTCTGATTAAAATTTCCTTTCTGAGTCCTAAA
TGCTTTAAATCTTCTTTTCCCATTCTTTTTACTTCTCCTATCCATAGTTACAAGTTCTTACGC
ATGACATATCTCTTGGCTGATAAGTTTAACTGCTTAAGCACCTGTTTATGTTTCATTTTTAAC
ATAGCCAGTTACTATTATGCTTGGATATACACAATGAGGGGAGCGGCCGC

FIGURE 496

TGTGGAAAAAACAGTTATTGCANCGGTTGCTTANAAAAACATAAAAATGCATCCATGGGGCTT
ATTTATTCAGGAGAAATCTCANAGCNCCTGGGAGTGCTTTANAGNCAGGGGNTGCTTGCATCC
TCTGTGGATGTGTGTGTGTGTGTTTGTGCCTAGGTGTGTGCGCACAGGTTTGTGTGCCTGTGT
GTGCATGTGTGTGGGGTGTGTGTGCATGTGTGTATGCACGTACCCGTGTGTGTGTGCACAGGT
GTGTGTGTGTGTGTGTTTGTGTGCCTGTGTGTGGGGTGTGTGTGCATGTATGCACGTACCAGT
GTGTGTGTGCGCAGGTGTTTGCGTGCACAAATATGCATCTGTGTGTATGTGTGTGTGTTCACA
CGTGTGTGTGTATGTGGCGGCCGC

FIGURE 497

CATTATAATTAACTATAGTTACTATGCTGTATATTTGATCACCCAGACCCATCTTATAACTGA
AAGTTTGTATCCTTTGATCCAAATCCCCACATTTTTCCCAGCCACTGACAACCACCACTTTAC
TCTGTTTCTATGAGTTCAACTGCTTTAGACTCCACATGTAAGTGAGATCATACAGTATTTTTC
TTTCTGCACTGGCTTATTTCACTTAACATAACATCCTCTAGGTTCATCTATGTTTCAGCGAAT
GGCAGAATTTTCTTCTTTTTAAAGGCTGAATAGTGTTCCCTCAGGTATATATACCAGATACAC
ATACATAAGGGAATATGTGTGTGTCTCGGGTACATGTACATAAGGGAATACTATTTTTTACTC
ATTCATGTATGTGTACCAGATACATATACATAAGGGAATATATGTATATGTGTCTGGTACATA
TACATGAAGGAATGCTATTTTTTACTCATTCATCTCTCAGTGGACACTTAGGTTGTTTTCATA
TCTTGGCTATTATGAATAGTGCTGCAATAAATATGGGAGTGGCGGCCGC

FIGURE 498

TTATTGGGAGATATCCATGTTTTTCATAAAATCAACAAGAGAATCCNTGATTGTTCAGAAGAA
AACAATTNTGACCGNAGAATGCTGTTACNTGAACCCCTTATTTCGAAGNATCATAAGATTCAC
AGGGGTGTTTGCATTTGGACTTTTTGCTACTGACATTTTTGTAAACGCCGGACAAGTGGTCAC
TGGGCACTTAACGCCATACTTCCTGACTGTGTGCAAGCCAAACTACACCAGTGCAGACTGCCA
AGCGCACCACCAGTTTATAAACAATGGGAACATTTGTACTGGGGACCTGGAAGTGATAGAAAA
GGCTCGGAGATCCTTTCCCTCCAAACACGCTGCTCTGAGCATTTACTCCGCCTTATATGCCAC
GATGTATATTACAAGCACAATCAAGACGAAGAGCAGTCGACTGGCCAAGCCGGTGCTGTGCCT
CGGAACTCTCTGCACAGCCTTCCTGACAGGCCTCAACCGGGTCTCTGAGTATCGGAACCACTG
CTCGGACGTGATTGCTGGTTTCATCCTGGGCACTGCAGTGGCCCTGTTTCTGGGAATGTGTGT
GGCGGCCGC

FIGURE 499

AAAAAAAAAAAAAAAAAGCTAAAAAACCTTGACTAAATCTACCATGTTTTCTCATATTATTAA
AAATTCTAAACGTGGGTTTTTTTGTTTTGTTTTGTTTTTCTGTTTCTCCCTCTGCAGAGTTGT
TAGCGGTTCTCGAGATGCCACTCTTAGGGTTTGGGATATTGAGACAGGCCAGTGTTTACATGT
TTTGATGGGTCATGTTGCAGCAGTCCGCTGTGTTCAATATGATGGCAGGAGGGTTGTTAGTGG
AGCATATGATTTTATGGTAAAGGTGTGGGATCCAGAGACTGAAACCTGTCTACACACGTTGCA
GGGGCAGGCGGCCGC

FIGURE 500

ATCAATGGCCACCCAGCAAGACCAAGTTACAAGGATCGTATNTTGGTCCGAAGGGATGAAAGT
GGCCCAAGGGTCTCCNTTNTCGGTGAACGTTCAGCTGNTGCAGGACCACGGGGAAATTGCCAA
GAGTAAGCATCTCCAGGGGGAGATGACCTAACGTTTCCAAAAGAGAAACAGGCAGCAGGTTCT
TAAGCAGTGAAGATGCGGACGAGATGTTGCATGTGGCTCCTGAGGCACAGCAGTGACTTCGTG
CCCAGAGCCTGGCAGAGAGGTCGCAGGTGTGCCAGCTTCCCTGCCAGTCAGGGCAGCCTTGGG
TGTGTGTGCAAGCATGTGTGCACATATTGTGTGATGTGCGTGCTCCTGTATGTGTGTGCATAT
GTGTGTATGCCTTGCACAGGTGTGCACAGGTCTGAATGTGTATACGTGGGGGGGGCGGCCGC

FIGURE 501

GAATATCCTGCAGGTATCTCTCCGGCCCACNTCCTTGCCTACTGAGCNTCAGCCCTGATTTGT
CATCGTCGGTTTCGTGACCCTCATCATATTTAAGCGGGAGCTGCACACGGCCCCCACACAGCA
GTGGGCACCAAGTACGGGATGCCCTCCAGCCATTCCCAGTTTATGTGGTTCTTCTCCGTCTAT
TCCTTCCTTTTCCTGTATTTAAGAATGCACCAAACAAACAACGCCAGGTTCCTGGACTTGCTG
TGGAGGCACGTGCTCTCCCTGGGACTCCTCGCTGTGGCCTTCCTAGTCTCCTACAGCAGGGTC
TACCTGCTGTACCACACCTGGAGCCAGGTGCTCTATGGAGGCATCGCTGGAGGCCTCATGGCC
ATCGCCTGGTTCATCTTCACCCAGGAGGTCCTCACCCCGCTGTTCCCCAGGATAGCAGCCTGG
CCTGTCTCCGAGTTCTTCCTAATCCGAGACACAAGCCTCATTCCCAACGTACTCTGGTTTGAG
TACACGGTAACCCGGGCAGAAGCCAGGAACAGACAACGCAAGCTGGGGCCAGCGGCCGC

FIGURE 502

CCCTGCCCAAAGTTAAGTTCAAGTTTTCTTTTCAGATAATGCCTGAAATTGCCCAGAATAGTC
AGAGGATTTAAAAATTTNTTTGACCACAAATGCACTAAAGTTTTAAGTAAAGCAGTTTCTTCN
TTCATTAGCATGTGTTTTACACTAACATTTAATAAGAAGCCATTTTTAGTCTTGATCTTGGCA
GTGTTTTCTTTAAGACTTCTGATGTTATCAAGTATTTCATTAAATATTAAATTATTATTAATT
ACTGTTAGTTTAAATATCATTAGGGGTTTCAATTTGGCTTCTTAAAATGGACTGAACTGTGGC
ATCACGTATTTTGTCTCATTCATGTATGAATAAAGCATAAATCAGTTTGTTAATGGATGCTCA
TACCACTGTTTATTTTTTCAAATATTTTAACACACTTTCCAAATGGTGGGATTTGCTTTATAA
ATACAGTTTTCTACTTACACATGAGGAAAATAATATTATTTGCATTATGGATGTACACTTTGA
AAAACTTTTCAATGCAATTATCTGTGTATTTCACAATCTCTGGTACTTTTCTCAGATTTAATT
TTGGTGGGGCGGCCGC

FIGURE 503

AAGCCTGTGTAAATGGATCAACCAATCCCAGTACATTTGCTTCAAGATTCAAACACATTCAGG
TGGGGGCTTGGGACGGGATCAGCATTCATCATGGGGAAGAAAACCACAGGCCATCAGTGGATC
ATACACAGTGCTCATCAAGAAAGATAACGTTACTTTTAAATTGTGGGCTCAAACTGGACAGCA
AGGTGCACAGTGGAAGAGAGCAGAAGTGTTTTTAGGCATTCGTTCACATACACAGATTGTCTT
CAGAGCCAAACGTGGTATCAGTTACATAGGAGATGTAGCAGTGGATGATATTTCCTTCCAAGA
TTGCTCCCCTTTGCTTAGCCCAGAGAGAAAGTGTACTGCTCATGAATTCATGTGTGCTAATAA
GCACTGCGTTGCCAAAGACAAGCTGTGTGATTTTGTGAATGATTGTGCTGATAATTCAGATGA
GACTACTTTCATTTGCCG

FIGURE 504

AAAAAAAAAAAAAAAAAAAAAACCTGCCAATTTTCAAACATACCGTAGAGATTATTTTCAGGTG
CCATTTTATAGTATAGCAGCAGGGCTTTTACTCTGTGTATGCACAGATGCAGTCTGGGGCATG
GTTTGTGTGCTGGACTTTCTCATGGCCATCATCAGTATGCTTATGGATTTGATGACAGGCATA
GCCTGGGCATATCACCTCATTGGTAAAGG

FIGURE 505

TTTAAGTGCAAAAAATTATTTTATTTTTTTCCCAGTAATTTTAAATTGGAATTCCAGCCNTGG
CTTATTTTTGGGAGACCCAGCCATNTACCAAAGCTGAAGGCACAAATGCTTATTCTCGTCACT
GTCCTTTTTATGTCAGCATTCAGAGTTACTGGCTGTCATTTTTCATGGGATGATTTTATTTGT
AGCTTTCATAACCTGTTGGAAGAAGTTACTACTTTGGACAGGCTATCAGGATAACTTCCTATA
TGAATGAAACTCTCTTATATTTTCCTTTTTCATCCCACTCCAGTTATACTGTGAGATCTAAAA
AAATATTCTTATCCAAGCTCATTGTCTGTTTTCTCAGTACCTGGTTACCATTTGTACTACTTC
AGGTAATCATTGTTTTACTTAAAGTTCAGATTCCAGCATATATTGAGATGAATATTCCCTGGT
TATACTTTGTCAATAGTTTTCTCATTGCTACAGTGTATTGGTTTAATTGTCACAAGCTTAATT
TAAAAGACATTGGATTACCTTTGGATCCATTTGTCAACTGGAAGTGCTGCTTCATTCC

FIGURE 506

TTTTTTTTTGACACGAGACATAAAAACTTTTAATGAAGGAGGACACAGNTCAGAGCCTTCCAC
AATGGGGCCAACCNTGCCCCACGGAGACCGGCCATGGCAACCGCTCAATCAGAAGGTGTTNTT
GATGCGGCCGGCCACCAGCCTAAGGATGTCCCCGATCTTNTTCTGCCAGTTGGCGATGTCCTT
GGACACGGCGCACCACAGCTCCCCATGCCGAGGCTNTGCACTCTCACAGCGCTTCCTCACCTC
CTCCTGNTGCTCCTCAGTGCCATGCTGCAGCTCAAACTTGTAGAAGAAGGCCCAGGCATCCCC
CAGGTCCGAGTCAATCTTCACAGTGCGGTGGAACCACTCCCTGGCCTTGGTGATCTTCCGCTG
ACTCCAAAACAGCTTGGCCACGGCCAGGAGCACATGGGGGTCATGCTCACACTTCTTCAGGGC
ATCCACGCTCTTGGTCCTCCTCTGGGGCCTTGCCTCGAGGAAGA

FIGURE 507

ACCCTGTTTTTTAAGCACACCTCAAGCGGGGCCTCGCTTACCAATANTTGATTAACCACAAGN
AAAAGTGTCAAGCTCAAGACGTCCTCCTTTTACTGTTTGTAAAACTGTCCTGAAAACTATGAT
CGACGTTCCGGAATTAGAAGGACGTGGGGCAATGAAAATTATGTTCGGTCTCAGCTGAATGCC
AACATCAAAACTCTGTTTGCCTTAGGAACTCCTAATCCACTGGAGGGAGAAGAACTACAAAGA
AAACTGGCTTGGGAAGATCAAAGGTACAATGATATAATTCAGCAAGACTTTGTTGATTCTTTC
TACAATCTTACTCTGAAATTACTTATGCAGTTCAGTTGGGCAAATACCTATTGTCCACATGCC
AAATTTCTTATGACTGCTGATGATGACATATTTATTCACATGCCAAATCTGATTGAGTACCTT
CAAAGTTTAGAACAAATTGGTGTTCAAGACTTTTGGATTGGTCGTGTTCATCGTGGTGCCCC

FIGURE 508

TCGACCCACGGGGTCCGGTAAAGTTGATGGTCTGCCTTGTACATCTCAACCATTCTTGAACCA
CTTAATCCTNTTTTTGNCAACACTAGTAGAACAGAATCCTGAAGATATGGAGACCTATACCTA
GATGTTGCTGAAGCTTTTNTGGATGTTGGTGAATATAATTCTGCACTTCCCCTCCTCAGTGCT
CTTTGTTTGCTCTGAAAGATACAACCTTGCAGTAGTTTGGCTTCGTCATGCAGAATGTTTAAA
GGCCTTAGGCTATATGGAGCGAGCTGCTGAAAGCTATGGCAAGGTGGTTGATCTGGCCCCACT
CCATTTGGATGCAAGGATTTCACTTTNTACCCTTCAGCAGCAGCTGGGCCAGCCTGAGAAAGC
TCTGGAAGCTCTGGAACCAATGTATGATCCAGATACTTTAGCACAGGATGCAAATGCTGCACA
GCAGGAACTGAAGTTATTGCTTCATCGTTCTACTCTGTTGTTTTCACAAGGCAAAATGTATGG
TTATGTGGATACCTTACTTACTATGTTAGCCATGCTTTTAAAGGTAGCAATGAATCGAGC

FIGURE 509

ACAGTATGGTCATTCATGCTCCAAAGAAAAGGAGATTGAGCTTTAAATNAAATNTCTCACAAG
TTAGGTGATCCAGGTTTTGTGGTCTTTGCAACCCTTGTGGTCATTGNGCCCTTGATATTAATC
TTCGGGGGGGTCCTCGCCATGGACAGACAAACATTNTTGTGACATAACAATCTGCTCTGTAAT
CGGGGCGTTTTCAGTCTCCTGTGTGAAGGGCNTGGGCATTGCTATCAAGGAGCTGTTTGCAGG
AAAGCCTGTGNTGCGGCATCCCNTGGTTGGATTCTGTTGNTGAGCCTCATCGTCTGTGTGAGC
ACACAGATTAATTACCTAAATAGGGCCCTGGATATATTCAACACTTCCATTGTGACTCCAATA
TATTATGTATTCTTTACAACATCAGTTTTAACTTGTTCAGCTATTCTTTTTAAGGAGTGGCAA
GATATGCCTGTTGACGATGTCATTGGTACTTTGAGTGGCTTCTTTACAATCATTGTGGGGATA
TTCTTGTTGCATGCCTTTAAA

FIGURE 510

TTGCTTGTTAAGCTAACAGGGGTGCAAGCTTCCATTTTGGATCTANTTTTAAATACACTCAGA
CAGGAGAAATTTGGANTAATTTTCAAACTACAGACACTTTNTAATCATGATGCATTTCAAAAG
TGGACTCGAATTAACTTGAGTTGCAAAACATGACAGTGCCCGAGGATGATAACATTAGCAATG
ACTCCAATGATTTCACCGAAGTAGAAAATGGTCAGATAAATAGCAAGTTTATTTCTGATCGTG
AAAGTAGAAGAAGTCTCACAAACAGCCATTTGGAAAAAAAGAAGTGTGATGAGTATATTCCAG
GTCCAACCTCCTTAGGCATGTCTGTTTTTAACCTAAGCAACGCCATTATGGGCAGTGGGATTT
TGGGACTCGCCTTTGCCCTGGCAAACACTGGAATCCTACTTTTTCTGGTACTTTTGACTTCAG
TGACATTGCTGTCTATATATTCAATAAACCTCCTATTGATCTGTTCAAAAGAAACAGGCTGCA
TGGTGTATGAAAAGCTGGGGGAACAAGTCTTTGGCACCACAGGGAAGTTCGTAATCTTTGG

FIGURE 511

AGTGGGCTTGAACTTCGTGAGTTTCGCTTTAAACTGCCCTTGAAATGAAGTGGACTTGGAGGG
GCATGGAATATTCACATGGNAGAGCCGCATGAGGCCGCCCACCACGCTTCNTGAAGGATGCCC
GTGGGAAGAATTTTGACGTGCCAGTGTCCTCGTTCTACAGGGTGTTCCATTCTTCCGCAATCT
CAGAAAAATGGGACTAAAAGAAACTTATTTTGTAAAATAAGAAGACTTCCATTTTTAATGACC
AACATGTATTAAGATGGACACCTACTCTACGAAACACGAAGTTCTATGGTCTCGAAGAAGCCC
GTGCCTGTTTGAAACTGATCCTAACTAAAAACAGACTTGAGTGGATATGAGAATGTTGGTTAG
TGGCAGAAGAGTCAAAAAATGGCAGTTAATTATTCAGTTATTTGCTACTTGTTTTTTAGCGAG
CCTCATGTTTTTTTGGGAACCAATCGATAATCACATTGTGAGCCATATGAAGTCATATTCTTA
CAGATACCTCATAAATAGCTATGACTTTGTGAATGATACCCTGTCTCTTAAGCA

FIGURE 512

TCCGGAACAATTATAATAAAGCCANCTTTAACCCATTGAGAGCATAAGGATGNTGCAAAGGCN
CAGTGCTGGATGGANAGGACAGTGCCTGGGGCAGTCATGGAAGACTTNTTTAGGAGGTGACTT
TTTAAGGGGTTTTGTGATCAAAANTATGGAGTCTTAAGTCCAACCAGTGGTTATGAATTCCGG
TTCTGCCACTTGCTATAATAGCTGTATCACCATGAGCGATAACTTAACCTCTTTGTGCCTCAG
TTTCTTCATATATAAAATGGGGATCATGATAGCTCTGTCCCAGGGGAGTTAGGAGGATTAAAT
GCAACAGTAATCCAACCCACAGTATGAAAAGACAGGCTAGCACATACAACACAATCTATAAAT
GTTTGCTATTATTGTCATCCTTTTTATTAGTATATCATGGTACAAGTTTGCTGGGTAGAAAGA
TGGCGATGGGGAAGGGGACATTTCAGGCCAATGTGATAATAAAATCAACAGACAAAAGAAGGG
AGAGTGTGGTGAGTAGGATAAAGCTCTGTACAGATGCAAG

FIGURE 513

ATTTAACTTTCCCCTTTAAAAGGAATTGGCTATAGAACTGCTTTGTAAAGATGCTTCTTGATA
TTTTACTTTTGTTCCTTTTCCCTAATCATTCCCTTTTTTCCCCACTCCTCCAGAA

FIGURE 514

TCCCGTGGGGGACTTGGGATCCCAGACGTTAAANTAGGAGCCGGAAAGAGGGAGGNTTTNTTC
TTGCCTGGAAGTTGCCTGNGTNTTTGTACCACCCCAGCCCCCCCACCGTGGNGGGACCNTCGG
CAGTGACGGCCCACAGTGCCACGTGNTCCCAGAACCCAGAGGGAAAGCATCACGGTTCNTNGT
TGACAGCTCCCAGTCACACAATCCCCACGTGTCCTGTCATTTCCTAAACAAGGTTTCATCACC
AGATTTAGACCCACCTGCTTTTCTCTCTTTTCTGCTTCTTCCAGAGATTTTTTTAGTGTCTTC
ATTTCACTGGTTACCACTTCTATCATGTTTCTGGCCCTTTCTTTATTCTCCTTAGCCTCATGT
TCTGTGGTATCCAGTTCTGACTTGACAGACATGAGCTTTTTCTCAGCTTTCTCCTTCATCTTC
TCCAGTTGGTCTCTGGATTTGTTTAGATCTTCAATGGCTTTAGTCTGTTCCAAAGTTTTAATC
TTCAGTTCATTGGTGTCGGCCAGTTTGGCTTTGAGCTCGGTGTGCAAGTCTCG

FIGURE 515

TCAGCCTTTCTATGGAAACAACTTTGAGGATGAGCCNCCTTTATTAAAAAAGTTAGGTATCAA
TTTTGACCNCATCTGGCAAAAAACACTAACAGTATTACATCCGTTAAAAGTAGCAGATGGCAG
CATCATGAATGAAACTGATTTGGCAGGTCCAATGGTTTTTTGCCTTGCTTTTGGANCCACATT
GCTACTGGCTGGCAAAATCCAGTTTGGCTATGTATACGGGATCAGTGCAATTGGATGTCTAGG
AATGTTTTGTTTATTAAACTTAATGAGTATGACAGGTGTTTCATTTGGTTGTGTGGCAAGTGT
CCTTGGATATTGTCTTCTGCCCATGGCGGCCGC

FIGURE 516

TTCATGGGAGGACATGGAGATCATGGGAAGCATATCTATGACTATAACCTAAAGCTGAAGCCG
TGTGATGGCCCAGTCTTGATTANTGAGCCAGCGCTGAACCCACTGGCCAACCGGCAACAGATC
ACGGAAATGTTTTTTGAGCATCTGGGTGTTCCTGCCTTCTATATGTCCATCCAGGCTGTGCTG
GCTCTCTTTGCTGCTGGCTTCACTACTGGCCTTGTGCTGAATTCAGGTGCTGGGGTTACCCAG
AGTGTGCCCATCTTTGAGGGTTACTGTCTGCCTCATGGTGTGCAGCAACTGGATNTGGCAGGC
CTTGACCTCACCAACTACCTCATGGTGCTAATGAAGAACCATGGTATCATGTTGCTCAGTGCT
TCAGACAGAAAGATTGTTGAAGACATCAAGGAGAGCTTTTGTTATGTGGC

FIGURE 517

ATATGTGAAATATTGGCAGTCGAACATGAACAACGGTCAAGATGTTCCAGGCACATAAGAGGC
GATTAGAGAGGCCAGGTTTATACACAATATACCATTTTCTGTAGTCCCTATTGTCATGGTTAA
ATTATTCTCTAAGTGTATTCTGGGTGCANAGANGCATGGGCTCTGTCAGTTTCTGGGAAACTT
TNTGCACCCTATAAACACAATATTTTTCTTTGTTTTCACACATTCACCATTTTGCTGGCACCT
TTNTGAAGTAGTGTTGTCCCGGTATCAGCCTTTGCAATATGTTANAGATGTACTGTCTGCCGC
ATTTTGCACTGGTTTTCTCTTTTCATTTATGATTAATAATGTGTATACGTTATTCCTTTTTAT
TATCTACTGTGTAAG

FIGURE 518

CCCCCCGCACCGATTTTTCAAAAAATAATTTTTCTAATTAAGATATGTGTATATGTTTTAACA
TCTTTCAGAAACATAAAATTGAATGAAAAGAGTAATTTGCAGAAACACATGCAATATAATTTA
TTGTGCATTTTTAAACACACAAAGCAGGACTACATGATGTTCATGTGTGCGTGTGTATATATA
TATATATTTAAACACACAGACAGGCCGGGCATGATGGCTCACGCCTGTAATCCCAG

FIGURE 519

GACCACTGGCCCACCCGCCAAGGATTGCCTAGATGATAATTTACAAGNACCACNACTTTAGAT
TTNCCTTATTGATGTTAAGATACCAAACCAAGTAAGTATTAAAATCAGCCAAACCTTGGACAT
TNTGGGAATATATAATCATTTGATAATGCATAAGAATAGGAAAAAATTGAATGTGTTTATGAC
TAAAGTTTTATATTTGTGGTAATGTTAAAATGTATTATTAAATATGTTAAAATTATTTCATTT
TTTTCCCCTTTGAGAGGTAAAGCCTAATACTTCTCCCCTTGAATATGGGCTAGACTTATGAGC
ACATTTCTAATGAACAGAGAAAGTGGATGTGGATGTGACAATGTGTATGTTGGAAGACTAGAC
AATATCAGAGATGAACATGATGGTGAAAGAAAATAAAAGAAGAAAGCTAGTTAATAAAAGGCA
CCATTGTTTCCTCCTCTTCCTCCTCCTCCACCTCTTTAACTCTCTCTCCCTCTCTCTGATCAA
CAGCTCTAGCAAAAGCCAGATGCTATGCGGTGCGGACTTTCAGGCAGCTTTGCAGGGAGATAC
ATGTGGCAAGGAACTGAC

FIGURE 520

TGGCTTGTAGCCCCATCCAAATAACAGCGGGGAGGAGCGGAGCCTGTGGTACGCAACCCATTA
CCCCNNTGATGAGAGAAAACTTTTATCCATGACCCAGGATGACTACAAACCATCTGATGGCCT
GCTGGTGACTGTGAACGGCAACCCCGTGGATTACCACACCATCCACCCAAGCCTGCCCATGGA
GAACGGCCCTGGCAAAGCCGACCTNTACTCCACCCCTCAGTACCGGTGGGAGCCCTCTGATGA
ATCCTCAGAAAAGCGAGAGGAGGAAGAGGAAGAGAAAGAAGAATTTGAAGAAGAAAGGAGCCG
TGAGGAAAAAAGAAGTATCAAAGTTCATGCCATGGTCTCCGTATTCCAATTTATTATGAAACA
AAGTTACATCTGTGCCCTCATAGCTATGATGGCCTGGAGCATCACCTATCACAGCTGGCTGAC
CTTCGTGCTGCTGATCTGGTCGTGCACTCTTTG

FIGURE 521

GAATTTTTTCGAAAAGCTAATGCCCCATTTTGGATGTCATTTACCATTCACCTTTTAATATTN
GGGGGCATTTTGGGATCAAATTATCCTGATGTTTTTCAACAAAGACTTGAGANAAAATAAGGN
GCATTACTTTTTTTGGACATTNTTCTTTTAGACCTATTGTGAGGTGTTTGCCCNCCATTAGAA
ATTNCCCCAAATGGTTGAAAATTNTTAAACAGNAGAAGGAAGAGACTCAAAGTTAGCATCACA
AAGAGAAACNCGATGCTGGAAAGGGAGATTGCATTCTCAATCCGGGATAATTTCATGCAGCAG
AAGGCTTTCAAGTACATGTCAGTGATTCAGGCTTTTCTCGGTTCTGTTCCACAATTAATTTTG
CAGATGTATATCAGTCTCACTATACGAGAATGGCCTTTGAATAGAGCATTGCTGATGACATTT
TCCCTGTTATCAGTTACTTATGGGGCCATTCGCTGCAATATACTGGCCATCCAGATCAGCAAT
GATGATACTACCATTAAGCTACCGCCGATAGAATTCTTCTGTGTCGTGATGTGGCGTTTTTTG
GAGGTTATCTCACGTGTAGTGACTCTGGCATTGTTCATTGCATCTCTGAAACTGAAGAG

FIGURE 522

AAATGTTTTGACAAATCACAAGAAAGTTTCAAAAATTTGGGNNTATTAGTTTGAAAAATTGTT
TTCAGTTCACTTGTGATTTCTTGTTTAATTCACTGCNGANAGGATTCTTTTANACTTTCCAAG
GATCTTAAAGCTATCNTACCTAGGAATGAGAATTATGGTGTTCCATGACAACTTTGAATAAGT
ATTCCCTAAAGCTAAGAGGAAATTCTNNCAATAATGANTCGGGNCATTGCTATTTTGGGAAAG
TAAAAGCGGAAAAAGCTTGACGACACTGAAAGGCTTGTTGAGATGGAACAAGTCCTCTCTTCA
CTTAACAAGATGAGAAAGACAATAGGTGGTGTGGCTCTCTGGCGACAGCAAATCTGCGCAATT
GCAAGGGTTCGCTTGTTAAAGTTAAAGCATGAAAGAAAAGCTCTTTTAGCACTGCTATTAATT
CTAATGGCTGGATTTTGCCCTCTTCTTGTGGAGTATACCATGGTGAAAATATATCAAAACAGT
TACACCTGGGAACTTTCTCCTCATTTGTATTTCCTTGCTCCTGGACAACAACCACATGACCC

FIGURE 523

CCTTATTGATGTTAAGAAACCAAANCAAGGTATGATTAAAAATCAGCCAAACCTTTGGACATT
CTGNGAATATATAAATCATTTGATAATGCATAAGATAGGAAAAATTGAAATGTGTTTATGACT
AAAGTTTTATATTTGTGGTAATGTTAAAATGTATTATTAAATATGTTAAAATTATTTCATTTT
TTTCCCCTTTGAGAGGTAAAGCCTAATACTTCTCCCCTTGAATATGGGCTAGACTTATGAGCA
CATTTCTAATGAACAGAGAAAGTGGATGTGGATGTGACAATGTGTATGTTGGAAGACTAGACA
ATATCAGAGATGAACATGATGGTGAAAGAAAATAAAAGAAGAAAGCTAGTTAATAAAAGGCAC
CATTGTTTCCTCCTCTTCCTCCTCCTCCACCTCTTTAACTCTCTCTCCCTCTCTCTGATCAAC
AGCTCTAGCAAAAGCCAGCTGCTATGCGGTGCGGACTTTCAGGCAGCTTTGCAGGGAGATAC

FIGURE 524

GAGGGTAGGATCCGCAAGCCCCTTTCGCGAAGCCCGAGNGAGNCCCGGGCGACAGGCAGGCAG
AGAATATGTTATTCCCATCCTTTGGCCCACAANATTTATGGCAGAGATGGTGGATTTCTTTAT
TCTCTTCTTTATAAAAGCAACCATTGTCTTAAGCATTATGCACCTCAGTGGGATAAAGGATAT
CTCTAAGTTTGCTATGCATTATATAATAGAAGAAATAGATGAAGACACATCAATGGAAGACTT
GCAGAAAATGATGGTTGTGGCACTTATATACAGATTATTAGTTTGTTTCTATGAGATAATTTG
CATTTGGGGAGCAGGTGGAGCTACCCCANGGAAGTTCCTGCTGGGGCTTCGAGTTGTGACATG
TGATACATCAGTGCTTATTGCACCAAGTCGGGTTTTAGTNATTCCTTCCTCAAATGTTAGCAT
TACAAC

FIGURE 525

CAAGATAAAATATATGGGGGAAGATGTAGAAATGTGACAGTTTGGCAAAAACAAAGTTCTCCC
AAGATTTCAGCACGTTTGCAGCGGAAATTCAGGAAACCATCNCAGCACTCAGAGAGCAGATAA
ACAAGCTGGAGGCACGCCTGAGGCAGGCAGGGTGTACAGATGTTAGAGGGGTTCCAAGGAAGG
CCGAGGAGCGCTGGATGAAAGAAGACTGCACTCACTGCATTTGTGAGAGTGGCCAGGTCACCT
GTGTGGTGGAGATTTGTCCCCCGGCTCCCTGTCCCAGTCCTGAATTGGTGAAAGGAACCTGCT
GTCCAGTTTGCAGAGACCGAGGAATGCCAAGTGATTCCCCAGAGAAGCGCTAATAAAAGTTTT
GTGCTGTTGAGCCCCAAATGGGAAATTTCTCAGGAAGAGACATTTAGGACTTCAGAACTTTTA
ACTTGTAGTCACATTGTTGATATGGAAACCACTGACTTAAGCAACTTAGTTCATCTAATCTTA
CATATACTTACGATCTTTTATTTTTTCATTTTCTA

FIGURE 526

GAAGTGAGGAGAAAGTTTATNTTTTTCATATAATTTAAGGGTCGTTTCTGTGAACCATTGCTT
CATGTCTTTTTCACTTTTTTCAATTGTCTCATTTTCCTCAAAATANAGGCACTGTTTATGTAT
TACAGAGATTAGGCCTTTGTCATTAGTCTTTTCCTGTGAACGAGATCACATAGATTATTTGTT
TCTTTTCTGGCTTTTGAATTTCAGCCATCATTTTAAAAAATACTTCCCCATGGTTTTTGTCCA
GTTCTTTTGTAACTTCTTGTTCTCCATTTCAATATTGGATGTTTGGCTTTTGTTCCTTTGCGT
GTTTGGTATGCGATATGGATCCCCCTTAGTCTTTTTGTCTAGCATCAATATATTTATTTTTAT
ACTGTCCTTCAGATTGATGATGATTTCCAGAGTTCTTGGGGCTTTAATGCCTGTTGCGTTTAC
AGACTCTCATCCGGG

FIGURE 527

CTTGTGTTTTCTTCCCCTCCCTAAATTTGAAGAACTATGGAGAAAATGGTACTTGATGACAGT
AGTGGTTTTAATAGGACTAACAGTACGATGGCAGTGTCTCTTAATTCTTATTCAGGTGCTGGT
AACCCGCCTATGTTTGGTGATTATGAAGCTCAGAGACACTGGCAAGAAATAACTTTTAATTTA
CCGGTCAAACAATGGTATTTTAACAGCAGTGATAACAATTTACAGTATTGGGGATTGGATTAC
CCACCTCTTACAGCTTATCATAGTCTCCTATGTGCATATGTGGCAAAGTTTATAAATCCAGAC
TGGATTGCTCTCCATACATCACGTGGATATGAGAGTCAGGCACATAAGCTCTTCATGCGTACA
ACAGTTTTAATTGCTGATCTGCTGATTTACATACCTGCAGTGGTTTTGTACTGTTGTTGCTTA
AAAGAAATCTCAACTAAGAAAAAGATTGCTAATGCATTATGCATCTTGCTGTATCCAGG

FIGURE 528

CCAGAATGAAAAAAAAAAGTCTTGTTGGATAATAGTGTTTGACTAGCGTTTTAAGAACTTGAG
AGTAAAAGCACCAATAAGATTTTTTCACTTTTTCCTGCTTCCACCCCCAAACTGAGAACATCC
ACTCAATTGTTTGGAAGAAACTGTAGGTCTATATAAATTTTATTTATAATGTATGTGTAATAT
ACATAATCATAATACAGTTCTCAGATGCAGGGAAGAAGTTTGGCATTTAATCATTGAGGCTTT
AGGTTTTTGATGTGATCAGACTGGGCCATGTCAAACCCGGAATTTTCACCAACAGTTCACTCA
CCCTCCTGGTACATTGCCATTCCAAGGAATTCTGAGAGTAGGCAAACAAATTTTGCCTTCATG
GTACAGTTCTCAGTTTTTCTTATAGGAGAAATATGGTATATGTTTATAAGAATCTTTTATGAG
ATTATAGATTTCAATGCTGTGGATAGTGTCTTGCACCCAAACAAGAAAGTCCATAATGGAATG
ATCTTCCC

FIGURE 529

TCCAAGTCCTTGAACATCTTTGGTTTTTTTGGAGTGTCCAAACCCATGTTCAGAAACGGCACA
TGGAATACTCATGTAATGNAGGAAAAGTCTATATCTGCAGCTGGACCCAGCCATACCAGGAGT
GATTTTGGAAATCCATACCCGTTTGGGATTGATCCGATTTGGAACTTGGCTTCAAACAAACTC
ACATTTNTGAACTCGTATAAAATGAAGATGTCGGTGATCCTGGGAATTGTCCAGATGGTTTTT
GGTGTCATCCTCAGCCTTTTCAATCACATATACTTCAGAAGAACTCTCAACATCATTCTGCAA
TTTATCCCTGAGATGATTTTTATCCTGTGTCTGTTTGGATACCTGGTTTTCATGATCATTTTC
AAATGGTGCTGCTTTGACGTCCACGTATCTCAGCACGCCCCCAGCATCCTCATCCACTTCATC
AACATGTTTCTGTTTAACTACAGTGACTCTTCCAACGC

FIGURE 530

GCCTTTAGTTTCCAGCTACTTGGAAGGTTAAGGTAAAAGGATCCCTTTGGGCCCGNAGGTTGA
GGCTNCAGNAGTTGAGATCNCACCATTGCATTCCATTTTGGGTGACACAAGCGAGAGCTATCT
CAAAACCAAAAAGCAAGCCAAANCCCACCCAGACCAAAAAGGTGACTTCCAGGGCTGCCCCAG
CTAGGAACACTCCAGAAAGCAGACAAGGAAAACCGAGTGTGAAGAGTCCCTTTGGAGATTGTC
ATGGCCATGTGACATTCCTTTGGCCTGAACTCAGTCACATGTCCCCTTCGAGATGCAGGGGGG
ACCTGGGAAATGTAGTTTCTGGCTGGGCAGCTGCTTTCCAGCAATAGCACTCTACTGCAGAAG
AGGAGCAGGAGTCTGTGGTGCAAAGCCAGCCAGGCCTGCCACAGATACTGCACCATTTACAAA
AATGCTTTTACACTCATTTCATTTGCTTCTCATCACAATCTATACCATCAGCTATACTGTCCT
CATTTTTCA

FIGURE 531

GAATGGAGGAAATTGCTTTCACTTCAAGACTTTCNTTTTTTCACTAAAACTTNTAAAGGTGTA
CAAGGGGAGGGAAGGGGGGCAAAGTCCTTGAACATTTTCTTTGGCTCGGCCATGTTATGATCA
TATACCTTTTAAATAAGGGGAAATAGTATCTTTAAAGTTAATGTCTAGCCAAGAGTTTAGTAA
ACGAAGAATTAAACTGCACTGTTGATCGGTGCTTTGTGTAAATACATCTTTAACATTTGGGTG
GAGAGGGGCCTTAAGAAGGACAGTTCATTGTAGGAAAGCAATTCTGTACATGAGTTTAAGCAT
TCTTGTTGCATTGTCTCTGCAGATTCTATTTTTGTTTACAATATTAAAATGTATGTTAGCAAA
ATGGGTGGATTTTCAAATAAAATGCAGCTTCCACAAAAGTTTTGTTATGGTATTCTGGTCTGA
GATGCATTTTCANTTTTCCNTTCTCTTTTTATTATCAATANTGTCATTTTTCCCTAATAAAAT
ATACCCAGG

FIGURE 532

GCTGTCCTGAGCAGTTGCAGAAGCATCGAGGGTGNAGAGGAGCACATACTGTCCATGGAGTGG
TGGTCAAGGTGGACAGGGGGCGGGTGGTGATGGCGCAGTTTGACATTGAATACCAGCGCCTAG
AGGCCTCCTATAGTGATTCACCCCCAGGGGAGGAGGACCTGTTGGTGCACGTCGCCGAGGGGA
GCAAGTCACCTTGGCACCATATTGAAAACCTTGACCTCTTCTTCTCTCGAGTTTATAATCTGC
ACCAGAAGAATGGCTTCACATGTATGCTCATCGGGGAGATCTTTGAGCTCATGCAGTTCCTCT
TTGTGGTTGCCTTCACTACCTTCCTGGTCAGCTGCGTGGACTATGACATCCTATTTGCCAACA
AGATGGTGAACCACAGTCTTCACCCTACTGAACCCGTCAAGGTCACTCTGCCAGACGCCTTTT
TGCCTGCTCAAGTCTGTAGTGCCAGGATTCAGGAAAATGGCTC

FIGURE 533

GGGTAAGTATATTCAGTGCAGGTAAAGACTGAATGAATGGGTACCATCAAATTGGTTAAATGA
AGATGGGTTTTGGCTCAGGAACACAAAGTNTTATTTTATCCTGTGCCAAACACTCCAGTTTTG
CAATGAGATTGTGAGGAAGGAGAAGGCAAGGATTCTGTTCCAATGTTTGGTCCCAGAGGACCT
AGAATAGTACTTTGACCGGGTAAGCGCTTAATAAAATAATGCTTACTCTTATGAATTTAGCTG
CAGAAACATTTAGTCCCATAGACAATATGTGTAGAATGTAAAAAATGCAAATCTTACTAAAAG
AATATACAGGAAAAGTTCTCCCTACTCCTTCCTGAAAGGGAGCCAGTGTTATTAGCTCGTCAT
GGAGATTGTCTGTGCTCATGCAAGCATCTCCCTGCATGTATGTCCTCTTGCTTTCGTGCAAAG
AATAGCATCCTACACACACCTTTTAGCCCCTTGCTTTTCGGTTTTGTGTATTTTGCAGATTGG
GTCATTTTGTGCACACAGTGCTATTTTATTCTTTTTTTTGTTTGTTTCCCCCTG

FIGURE 534

ATCATAGTGTTTTCAAACTCCCCGTGTAAAAGTTCCCAAAATCCCATGTCACAGNTGAGTCTT
GGTTTTGTTGATTGGTTTGTCTCTTGANAGTGTGTTATTTTTTTGTTTCATTATGTGTCTCATA
ATTTTTGGTTGAAAGCTAAAGCCTTCTTGNGAAGGCTAGTGGAGACTTGGGTAAACACTATTT
ATGNGCAAAAATGGACATGCCTTTTNTTTAAGGAGGAGGCATTGAGACAACTCTGTCAGGTTT
TGTTGTTAGTATGGTTACTCTCAAAAAGNACATAATTCAAATTCTTCCAGTATTATTTTTTTG
CTTAGTGGCTGGTTTGTTGGAGAGTTTTTCTCAGTGTCTGTTCAAATCACAGTTATTGGTCTT
TTCTTTGTGCCTACGTNTAANAGAGGATATCTTTCTGTGCTTTTACCCTCACTCTTCCAGCAG
TANACTGCTGTTACTTGTTCC

FIGURE 535

CTGCCCATTTTTTTGCTTTTACCTGGCAAGTGTTTAAAAAAGGCCTCAAAGAAAAGGGGTTTG
TGTTGCTAGTTAAGCTAGCTTGTATTGTGGNGGCTTCCTTCGTTTTNTGCTGGCTGCCATTCT
TTACAGAAAGGGACCAACCCCTGCAGGTTNTAAGAAGACTCTTCCCGGTTGATCGTGGATTAT
TTGAGGATAAAGTAGCCAATATTTGGTGCAGCTTCAATGTCTTTCTGAAGATTAAGGATATTT
TGCCACGTCACATCCAATTAATAATGAGCTTTTGTTTTACGTTTTTGAGCCTGCTTCCTGCAT
GCATAAAATTAATACTTCAGCCCTCTTCCAAAGGATTCAAATTTACACTGGTTAGCTGTGCGC
TATCATTCTTTTTATTTTCTTTCCAAGTACATGAAAAATCCATTCTCTTGGTGTCACTACCAG
TCTGCTTAGTTTTAAGTGAAATTCCTTTTATGTCTACTTGGTTTTTACTTGTGTCAACATTTA
GTATGCT

FIGURE 536

GGTTTGTTTCCCCATCTGCCATATTATAAGTTTTTTGAGGCATCCCCAGCCATGCTGAACTGG
AAGTGGCACTAAGGTCCAAAGGAAGCTACATATGGGTGGTCCCTGTTACACCAGCCTCCCAAG
CCTCCCAGTGCACCTTCTAGGAGACAAGCAAGGAAGGCCGCTGCTTGTTTGTCATCCTGCTCA
TGGCGGTGTACTGGTGCACGGAGGCCCTGCCGCTCTCAGTGACGGCGCTGCTGCCCATCGTCC
TCTTCCCCTTCATGGGCATCTTGCCCTCCAACAAGGTCTGCCCCCAGTACTTCCTCGACACCA
ACTTCCTCTTCCTCAGTGGGCTGATCATGGCCAGCGCCATTGAGGAGTGGAACCTGCACCGGC
GAATCGCCCTCAAGATCCTGATGCTTGTTGGAGTCCAGCCGGCCAGGCTCATCCTGGGGATGA
TGGTGACCACCTCGTTCTTGTCCATGTGGCTGAGCAACACCGCCTCCACTGCCATGATGCTTC
CCATTGC

FIGURE 537

TTGGCCTAATTTAAGTGATATAAAAAATGAAATTTTTATGCAGTGTGGGNGAGGGGCAAAAA
AAAATANATTTGAACACCCAGATTTTAGTTTTGGCTCTGTGNTTGCAGCTAGTTACATGGCAT
CCAGGACNAAAGTTTGGAAAACAAAATAATGGAACTAAATAGTACTAACCAAAGTATAGGGTG
CTTTATGATTTACAGAACTCTCTTACAGGCAGTATGTTGTTCAGGCGCCACTAGAACCCACGT
AATGGCAGAGGCTTCCTGTTCCATGTTTAAAAACCTTTCCAAGGCTTTTCATTATTTTCTTAT
CTGTGGTACCCCTAGCTTCCTGTGCTCTAGACACACTGGCCTACCTTCAACTTCCTTGACCAG
TGTAGCTTACAGTGTAAGCTTACCCCACACCCCCACCTCCTGCAATAAAATAGTAGCATCGGC

FIGURE 538

GGTAATGGGCAATTAAAATTTTTTCGGGTCTGGATTTTAAAAATTTATATTAAGGNATTGAAG
TTCCTTTTCTCCNTTAGGTTTAACAGTGAATTCACATGAGTAATTTTTAAAAGATATCAGATN
CATTTTGCTATTCAAAGAAAATTATGATTTAAAGCCACTTTTTAAAATNCGAGAAGGAAAATA
GGATGGATTAAAGGGTTAACTTTTAAAGATTATTATTGGTTAATGTTGACATATTTCCTCTAT
CTCATAGATGGTAAAAGTGTTGCTTTTAAAAACTGGCAAATGCACTCTTCAGAAATCCTTTTC
TATCTGATCCACATGGAGAGGTTAAAGGTTCAATTTCATGACCTCTATGCAGGCAGCGCTCTC
ATTGGATGTAAGAATATTACCTGCAAGGATAGAATGCAGTTGTGCAACAGAGACACATTCTTA
TTTCACTTTTTTCACAATTTTGTTTTGTTTTTAATGACCCTTTTATTGAATATTGG

FIGURE 539

AAAGGGTCCGGTCCCCGGCCGAAACCACTTTTGATCTTTCCNTCTTTGGGCTCAAAAAATGTA
CAGGTTTTCCAGGGCAGCCTTGGGATTGGGCCACTTCCTTTANGATCCTGGTTCTTCCCGTTG
TCTTTNANACGGAGAAGTTGCAAATGGAGCAACAGCAGCAATTGCAGCAGCGGCAGANACTTT
TAGGCCTAANACAGGGCTNTCAGGAGGAATGCCAGGGGCTTTACCCTCACNTCCTGGAAANAT
NTANATTGTTATTGCNGTTTGAGCTGTCTCAGTGGGATAAGTTTGAAATTCAAGNGTTTGAAC
TGNTGAAAATTGGAATTTTTTTTTTAACTTTGGCAGCAANGGGTTCG

FIGURE 540

GGTTTGCTTTGGGGGTGTTTTTGGAATATTTTGTGACTGCGNCNTCNTAGGGTCACTGGCATT
TTGNTTAGCTATAAATTATAAACAGATGGAACTTTACCACGCCTTGCCATTTTTTTGCTTTTT
ACTTGGCAAGTGTTTTAAAAAAGGCCTCAAAGGAAAGGGGTTTGTGTTGCTAGTTAAGCTAGC
TTGTATTGTTGTGGCTTCCTTCGTTCTCTGCTGGCTGCCATTCTTTACAGAAAGGGAACAAAC
CCTGCAGGTTCTAAGAAGACTCTTCCCGGTTGATCGTGGATTATTTGAGGATAAAGTAGCCAA
TATTTGGTGCAGCTTCAATGTCTTTNTGAAGATTAAGGATATTTTGCCACGTCACATCCAATT
AATAATGAGCTTTTGTTTTACGTTTTTGAGCCTGCTTCCTGCATGCATAAAATTAATACTTCA

FIGURE 541

CCTTCCACTTATGTGGTCCCACACCACCCGCCTCCCCTGCCAGGNTTTATTTNGNGTGTGTGT
GAGTGTGTTCTGTTTTGTGTTTTGTTTTTTGNTGTTGTTTTCAGTTGTTTGGTTTTCTTTTCT
TTCCCCCCTCCGGTCCCATACTTCACAGCACTCTGGTGCGGGAAGAAGCAGAAG

FIGURE 542

TCTAGTTTGCCTAAGTAGAATTTACATGGGAATGCACTCTATTCTGGATATTATTGNTGGATT
CCTATATACCATTTTAATCTTAGCTGTCTTCTATCCATTTGTGGACCTGATTGACAACTTCAA
CCAAACTCACAAATATGCTCCATTCATCATCATCGGGCTTCATTTAGCTTTGGGGATCTTTTC
TTTCACTCTTGACACCTGGAGCACATCCCGAGGAGACACAGCCGAGATACTAGGAAGTGGTGC
TGGAATTGCATGTGGATCTCATGTTACTTATAACATGGGTCTAGTATTAGATCCTTCTCTAGA
TAC

FIGURE 543

AGAACCCCCCGGTGAAGTTTTCCGCCAATAACCTAAGGGGGCTTTTTCCAGGACTTCAACCCG
AGTAAATTCCTCATCTATGCCTGTCTGCTGCTTGTTTTCTGTGCTGCTGGCCCTTCGTTTGGA
TGGCATCATACAGTGGAGTTACTGGGCTGTCTTTGCTCCAATATGGCTGTGGAAGTTAATGGT
CATTGTTGGAGCCTCAGTTGGAACTGGAGTCTGGGCACGAAATCCTCAATATCGAGCAGAAGG
AGAAACGTGTGTGGAGTTTAAAGCCATGTTGATTGCAGTGGGCATCCACTTGCTCTTGTTGAT
GTTTGAAGTTCTGGTCTGTGACAGAATCGAGAGAGGAAGCCATTTCTGGCTCCTGGTCTTCAT
GCCGCTGTTCTTTGTTTC

FIGURE 544

TTAATGTCTAAGCCAAGAGTTTAGTAAACAAAGAATTAAACTGCACTGTTGATCGGTGCTTTG
TGTAAATACATCTTTAACATTTGGGTGGAGAGGGGCCTTAAGAAGGACAGTTCATTGTAGGAA
AGCAATTCTGTACATGAGTTTAAGCATTCTTGTTGCATTGTCTCTGCAGATTCTATTTTTGTT
TACAATATTAAAATGTATGTTAGCAAAATGGGTGGATTTTCAAATAAAATGCAGCTTCCACAA
AAGTTTTGTTATGGTATTCTGGTCTGAGATGCATTTTCATTTTTCCTTTCTCTTTTTATTATC
AATATTGTCATTTTTCCCTAATAAAATATACCCAGG

FIGURE 545

AGTTTCATATATTTGGGAATGAGCCTTGAGCCATAAAAGGTTTTCAGCAAGTTGTAACTTATT
TTGGCCTAAAAATGAGGTTTTTTTGGAAAGAAAAAAATATTTGTTCTTATGTATTGAAGAAGTG
ACTTTTATATAATGATTTTTTAAATGCCCAAAGGACTAGTTTGAAAGCTTCTTTTAAAAAGAA
TTCCTCTAATATGACTTTATGTGAGAAGGGATAATACATGATCAAATAAACTCAGTTTTTTAT
GGTTACTGTAAAAAAGACTGTGTAAGGCAGCTCAGCACCATGCTTNTCGTAAAAGCAGCTTCA
ATTATCCNCTGGGGTTATCTTTTGACAACTTGCCATTATCTGATGTTACACAATTCAATAGCA
AGCAAGTTTGAGACAATCGC

FIGURE 546

CATAAATATACCCACCCCAAATGGACGACTTATGAAGGAATTNCTTGTGAAAGCTCATTGGAG
TAAAATTTCCTCTCAAACAATACTTTTAGGTCATANGCNTGAGTCTATTAATTATTTTTCTGT
TANACCCTGCCAAAAAAGAATTTTAAAAGTTAGTTTATGTTTTGTGTAACCATGTTCTTCAGA
ATGCAGGTATGTGAGCATCATGGTTTCTGGGTAATTCTGCTGCTCCTGTCTTTGAAAATGGAG
ATACCACTTGCAGCTTATCCCACTGCTGAGTATTCCAGCATTGGTAGTGGTTTCACTCCATTG
CATCCATCCAGAACTTTCACACAGGCCTCCCCCGAACCCCTTGCGGCGCAAGGGGTTCG

FIGURE 547

AAAAAAAAAAAATTAAGTGAACCTCTACTTTAGAATGTTGGCTTTTCATATATGTACAAAACA
AAAGAGGTTGCAGTGATGGCGTGGATAAAGGCACCTGTGTACTTTTCCAACCTATCCAATTTC
AAGATGTATCCTTTGTGGATTACATTGGTTCTTTTCTATGGAATCATGCACCTTAGACCTGGG
AGAAACCAGCGTGACATCCAGGGTCAAGGTTTTCCAATCAGGTATTTTGGGCAAGGGGTTCG

FIGURE 548

AAAAAAAAAAAAAAAAAAGCTAAAAACCCTTGACTAAATCTCCCATGTTTTCTCATATTATTA
AAAATTCTAAACGNGGGTTTTTTTGTTTTGTTTTGTTTTTCTGTTTCTCCCTCTGCAGAGTTG
TTAGCGGTTCTCGAGATGCCACTCTTAGGGTTTGGGATATTGAGACAGGCCAGTGTTTACATG
TTTTGATGGGTCATGTTGCAGCAGTCCGCTGTGTTCAATATGATGGCAGGAGGGTTGTTAGTG
GAGCATATGATTTTATGGTAAAGGTGTGGGATCCAGAGACTGAAACCTGTCTACACACGTTGC
AGGGGCATGCGGCCGC

FIGURE 549

AAATTATCTTTACTGATATGCGTTGCCAAATCCCATGAGAAAAGACATCTCATTTGAGGTTCC
CCTTCCTCTCATGTGGTTGATTTTTTGGAAGGTGATACAGATGTGGGTAACCATGCAAATGTT
TATGAATAACTTTACTGAAGTGATTCCATCCGTATTCTGTTCTAATACTTGGAGAATGACCTT
CATATTTATATATTTTATTTCTTTGTTTCAACTATCCAG

FIGURE 550

TGAAGATATGGGAGACCTATNCTTAGATGTTGCTGAAGCTTTTCTGATGTTGGGAATATAATT
CTGCACTTCCCCTCCTCAGGGCTCTTGTTTGCTCTGAAAGATACAACCTTGCAGTAGTTTTGG
CTTCGTCATGCAGAATGTTTAAAGGCCTTAGGCTATATGGAGCGAGCTGCTGAAAGCTATGGC
AAGGTGGTTGATCTGGCCCCACTCCATTTGGATGCAAGGATTTCACTTTCTACCCTTCAGCAG
CAGCTGGGCCAGCCTGAGAAAGCTCTGGAAGCTCTGGAACCAATGTATGATCCAGATACTTTA
GCACAGGATGCAAATGCTGCACAGCAGGAACTGAAGTTATTGCTTCATCGTTCTACTCTGTTG
TTTTCACAAGGCAAAATGTATGGTTATGTGGATACCTTACTTACTATGTTAGCCATGCTTTTA
AAGGTAGCAATGAATCGAGC

FIGURE 551

TGGACCCCAGTTGTCAGCTGGGNGGTACTGGATCATCTTTNTTCTATCACAAGATAAACTATC
AANTTCCCCAGCATCATGACCTTGTTGCCGTAAAAAGGAGTTCACTACTTCTGTTCACTTTGA
GTCTCTTCAAATGGATTCTGTGTCCTCCTCTGGAGTCTGTGCTGCATTTATTGCTTCTGACTC
TTCCACTAAGCCAGAG

FIGURE 552

CTAAAGGGGAAGAAGAAAAAGAAAGGATTGGTCTTGCTNTAAGGGGTAGAAAAGNGCAAGGGG
AANCAGGAAAGGAAGGCNCCCTACGGNGTAATTATGAAAATGCATTGGAACTTCTGTCTGATG
TTTTGCTTTTTTTTTCATTTCTCAAAATATTTCTANANANGGTNTTAATCCTTCTTCCACCAT
TTGCTTTAGTTTTAAGNGCCCTGTGTGATAGAAGGGTTCATGTTGTAAAATCAGTNTTGAATA
ATCAGAACACTTCTACCAGATTGTCTAATGTTGATTTGTTTCTGGCACTGCTTCTAAATGTCT
TCCTCCTCATTCTGCG

FIGURE 553

TAAAAGAAAAGCTAAAGTTTTACTGTGGCCAAAAAACCCCTACATGGTCTGGGGACTGGNGGT
NTCTTTGACCNTATCTTTGACCACTTTTCTTTTTTCANTTTTCTCAAGGCACANCTGGCCTCC
TTTTTGTTCCTGGCANTGGGAAGACTTGTTCCTACTTCAGGGTCTTCATGTTTGTTCTTCCNT
CTGCCTTGAACACCCACCTTTCTCCCAAGTGTTCCAGGCAGATGGAGTATGCACATGGCTCAC
TCTTTTACTTTTTAAGTCTCTGCTCAAAAGCAAATTTNTCAGCCATGGCTTTCCTGAGCACCC
TATTTAAAATTGCTTTCCTACTCCTACATGGCTGTTCTCCTTTGCTTACCACCAC

FIGURE 554

TTAAAATAGTAAAAAAAAAAGAATTTATTTTTGTTCTTTGTTAGAATTTCTCTGCAAAGAATG
TCCAAAAATTCATATTCACATTGATCGTATGGCAAAAAGATGTCCCAGAAGAACAAGAACATA
TGAGAAGATGGCTGCATGAACGTTTCGAAATCAAAGATAAGATGCTTATAGAATTTTATGAGT
CACCAGATCCAGAAAGAAGAAAAAGATTTCCTGGGAAAAGTGTTAATTCCAAATTAAGTATCA
AGAAGACTTTACCATCAATGTTGATCTTAAGTGGTTTGACTGCAGGCATGCTTATGAC

FIGURE 555

CCTTATTTTCCATTCCAAATGGCAGCCAGNATAAAATTNATTTCCCACAATTTCCCTTTAANG
GTAAGGGTTGCCCTTNCCGCAATGCCCCTCACATGGTTCTTTTGGNCAGTTCGGAAGCCCTTG
GGNTCTTGATGGCTTTGTGTCTAGTAATAATGCAGGGTGCTCAAGGAAATAAATTCAGTGTGG
ATATACTGAAAAC

FIGURE 556

GGTCCGGAATAAGCCATTAGCAATCCTTGCTGTATCCAGGCCTTATTTTTTATAGACTATGGA
CATTTTCAATATAATTCTGTGAGTCTTGGCTTTGCTTTGTGGGGTGTTCTTGGAATATCTTGT
GACTGCGACCTCCTAGGGTCACTGGCATTTTGNTTAGCTATAAATTATAAACAGATGGAACTT
TACCACGCCTTGCCATTTTTTTGCTTTTTACTTGGCAAGTGTTTTAAAAAAGGCCTCAAAGGA
AAGGGGTTTGTGTTGCTAGTTAAGCTAGCTTGTATTGTTGTGGCTTCCTTCGTTCTCTGCTGG
CTGCCATTCTTTACAGAAAGGGAACAAACCCTGCAGGTTCTAAGAAGACTCTTCCCGGTTGAT
CGTGGATTATTTGAGGATAAAGTAGCCAATATTTGGTGCAGCTTCAATGTCTTTTTGAAGATT
AAGGATATTTTGCCACGTCACATCCAATTAATAATGAGCTTTTGTTTTACGTTTTTGAGCCTG
CTTCCTGCATGCATAAAATTAATACTTCAGCC

FIGURE 557

AAATCTTCTTGAGCTTTGTTTTGAGATGTAGTTGAGTTAACTTATAAACCGTTTCATTCTTTT
GGGTNTTGTTTTTATGATTTATTAGACAGATATGAAGGAGTGCTTAGTCCAGGANTAATTATT
CCTCACCACTGAGGCAAGACTTTCTGTGGACTCTGTTGAATGTTCCATGAATTAATAGTTTTC
CCAGTTTGGCTAGTGGGAACAGATACTATTCCTGGCTTTGTATGAGTATCAGGCCCTGTTCCC
TCCCATTGTTTCTGATGTTCTTTTTCTGGATTCTCATAGTTTCCTCATATGCATATGCTGATC
AGTTATCTGGTGAATGCTTGAGAGAAGATCTCTATAGACCTCTGGGGTTCTTTTCTATGCAAC
TGTCTCCTCTCAGCATTCTGTGCAGTTATTCCTTGCTGCTTTTTTCTCTCCTGGCTCTTAACT
TTCTCTTTCCAACTCAGGAGTCAGCTGAGATTTGCCTCAGTTGCCAC

FIGURE 558

TTGCCCTTGGGAGTAAACCTTGAATNATTTTAAAAAAACNACGGTTTTAAACCTTGGCNACCG
TTGGGTTGAGGCCTTGACCACCTTTGGGACACCNTGCAAGAGGANTCCAACCCNAAACAACAA
CCAGGATGTGCTCCNAGCCCAGCCCGGGGNTTCAGTNCCATANTTTGCCATGTGTCTGTCCAG
ATNTGGGGTTGAGCGGGGGGTGGGGNTGCAACCCAGTGGATTGGGTCACCCGGCAGACTTAGG
GAAGGTGAGGCGANGTGGGGAGTTGGCAGAATCCCCATACCTCGCAGATTTGCTGAGTCTGTC
TTGTGCAGAGGGCCAGAGAATGGCTTATGGGGGCCCAGGTTGGATGGGGAAAGGCTAATGGGG
TCAGACCCCACCCCGTCTACCCCTCCAGTCAGCCCAGCGCCCATCCTGCAGCTCAGCTGGGAG
CATCATTCTCCTGCTTTGTACATAGGGTGTGGTCCCCTGGNANGTGGCCACCATCATGTCTAG
GCCTATGCTAGGAGGCAAATGGCCAGGCTCTGCCTGTGTTTTTCTCAACACTANTTTTCTGAT
ATGAGGGCAGCACCTGCCTCTGAATGGGAAATCATGCAACTACTCAGAATGTGTCCTCCTCAT
CTAATGCTCATCTGTTTAATGGTGATGCCTCGCGTACAGGATCTGGTTACCTGTGCAGTTGTG
AATACCCAGAGGTTGGGCAGATCAGTGTCTCTAGT

FIGURE 559

ATCCGGCTGGGATACAATTTTCATCTTCCATTTNACTCTTGTCAATTCCACCTTTTAAGAAGA
CAGCNTNTCATTCCTGAGGCATGAAAATTCTCCAGGGACAAAGCCATGCNTCAGTNACATGTG
TGTGCAGAGAGAAATGCACCTGTNTATCTAAGGGTAGATTTTTGATCCCTGAATAATTCATTG
ACTAAACTGACCTCTTCCTCCTGGCTAAATAAATTAATTTTGCTGGCTTCTCTCTCAGCGGTT
TCTATTTTGTAAATTGCTGCATGACCAAAATAGCCCCANTCAAAATCAATTGGATTAATNTTA
ATGGTTTGGTTGGATGAATATTCTTGGATGAATATAAAATGTGCTGCCCTTCACAGATGACAC
CACTCCCCTGTCAATCATAGCACATGTGTACTTTTTATTGTTACTTAATAGTGATGGATTTGC
ACTTTTCTATCCTCATACTCTTTCCTGTTTTCTTCTTTGTACAATTGCATGCAGGAGGGCTGG
ATGCCAGGGTTAAGAGAGAAATTCATGACAAGGAAGGTAAAATTGGTTCAAATGAGCATGTGT
CCCACAGCCTTAGTCTCCC

FIGURE 560

CCGGGAAATTAAGCCCTTTTTTTTTTTTCAAATAATAAAAGCTTCGAAATTGAAAGGGAGAAG
TAAATATNCCGGATACCATGATTTAATATGTAGAAATTNTAAGAGATTCNCAAACCATTAAAG
ATAAAAGCCAGTTCACCAAAGTNAAGGATGNAAGATCAGTGTACATAAATCTGTTTTATTTCC
ATATACTTGCAAAGAGGAATCCCAAAACTGAGATTGAGGAAAGCATATATAATAGCATCAAAA
AGTAGTACAAAACATATACTCTGAAAACTGCAGAATGTTGAGAGAAATTAAATAAGTAAATAG
ATAATCCCATGTTCATCTAGCCAGAGGACTCATGTATTTTGGTTATTAACCCCTGATCAGATG
TATGGTTTGCAAATATTTTCTCCCATTTCATACATTGGCTCTTCATTCTGTTGATTGTTCTCT
TCCTGTACAGAAGTTTTTAAGTTTCATATATAATTTTAGTGGTCTATTTTTGCCTTCGTTCCC
TATGCTGTCGGGGTCATATCTAAAAAAGGTCATCGTGCAGACCAACGTCATGGAGATTTTCCC
TGTGTTTCCAGTAGTTTTACAGTTTTGGGTCTTACATATAAGTTTGTTTTCTTTTTTTCGAGA
TGGAATCTTGCTCTGCGG

FIGURE 561

AAAAAAAAAAAAAAAAAGGGCGGCCGCGACTCTAGAGTCGACCTGCAGGGTTTTATCCAAAAT
GAAATGGTTGGGCACCAAAGAGACAGAAACCCACAAGTCAACCACTTAGGTCACACATGGTTC
TGAAAGTCCTATACTGTTCTGGATTCCCAGGCACAGAACTCCGGGCTGCTCAGGAAGAGACTA
TGATTCTTCCACCTGCCAGCTACTATTGGCCATCCCTTCTCATTGCTTCTAGCTCCAGCCTTC
TCATCCCAATTCTCTATTCTACATTGTTATTTCTAACCCATTGTGTGCTGGGAAATCAAACCA
CTCAGCA

FIGURE 562

CCCACGCGTCCGNTGGTGGCTTCAGAAGAAATTCTCAACACCTAGCTCGCCAGAGAGTCTATG
TATGGGATTGAACAATCTGTAAACTAAAGGATCCTAATCATGAAAATAAGTATGATAAATTAT
AAGTCACTATTGGCACTGTTGTTTATATTAGCCTCCTGGATCATTTTTACAGTTTTCCAGAAC
TCCACAAAGGTTTGGTNTGCTCTAAACTTATCCATCTCCCTCCATTANTGGAACAACTCCACA
AAGTCCTTATTCCCTAAAACACC